The potential of body weight change and glycemic control as markers for early detection of pancreatic cancer in the diabetic population

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Summary

Pancreatic cancer is a devastating disease with poor prognosis. In fact, it is associated with one of the lowest survival rates of all cancers. Early detection of pancreatic tumors is the key to sustainably reducing pancreatic cancer mortality. Thus, effective screening programs are eagerly awaited enabling disease detection at an early stage when patients are still free from subjective complaints. Patients with a new onset of diabetes mellitus (DM) represent a known risk group for pancreatic cancer. Long-standing DM is also associated with the development of pancreatic cancer, although to a lesser extent. Given the huge number of individuals with these conditions, further risk stratification is needed to enrich the population to be screened for pancreatic cancer.

This thesis aimed to contribute to the establishment of groups within the DM population that are eligible for pancreatic cancer screening. The thesis comprises three studies, two case-control studies and a descriptive study, using data from the United Kingdom-based Clinical Practice Research Datalink GOLD. The primary care database contains anonymized electronic health care records of millions of patients who are registered with some 700 different practices.

Study 3.1 characterized the role of body weight change and blood glucose concentration as markers in the early detection of pancreatic cancer in patients with new-onset DM. Blood glucose levels and weight change before the onset of DM were compared between pancreatic cancer cases and controls. The study provided evidence that weight loss and blood glucose levels in the normal range (i.e. absence of pre-diabetes) before the onset of DM may be predictive of pancreatic cancer-associated DM. In particular modest weight loss before the onset of DM was identified as a potential early marker for pancreatic cancer.

Study 3.2 evaluated the role of glycemic control and body weight change as markers in the early detection of pancreatic cancer in patients with long-standing DM. HbA_{1c} levels, blood glucose levels, and weight change before cancer detection were compared between pancreatic cancer cases and controls. The study showed that poor glycemic control (HbA_{1c} ≥ 8%) may help identifying patients with long-standing DM at risk for pancreatic cancer at an earlier stage. More importantly, in this study, HbA_{1c} values of ≥ 8% were associated with an increasing risk of pancreatic cancer with closer proximity to the cancer diagnosis in the 4 to 5 years before cancer detection, indicating that in particular DM deterioration may serve as an early marker for pancreatic cancer. Furthermore, an increased risk of pancreatic cancer was

observed in patients with body weight loss in the past 3 years, with adjusted odds ratios increasing with increasing weight loss.

Study 3.3 assessed glycemic and body weight patterns in patients with pancreatic cancer-associated deterioration of DM. Non-cancer patients with DM progression were used as a comparison group. The study revealed that steep increases in HbA_{1c} levels and loss in body weight occur distinctly more often in association with pancreatic cancer-associated DM deterioration than with typical type 2 DM progression. Also, persistent elevation of HbA_{1c} after DM treatment intensification may be a characteristic feature of pancreatic cancer-associated DM deterioration.

In summary, the large population-based studies conducted in the context of this thesis, provide important data for the establishment of groups within the diabetic population that are eligible for pancreatic cancer screening, thereby contributing to the challenging task of disease detection at an early stage (i.e. when patients are still free from subjective complaints). Some results may be of immediate relevance for physicians. Others may trigger further research.

Abbreviations

AOR	Adjusted odds ratio
CAPS	Cancer of the Pancreas Screening
CPDPC	Chronic Pancreatitis, Diabetes and Pancreatic Cancer
CPRD	Clinical Practice Research Datalink
DM	Diabetes mellitus
ENDPAC	Enriching New-Onset Diabetes for Pancreatic Cancer
EUS	Endoscopic ultrasonography
GPRD	General Practice Research Database
HbA_{1c}	Glycated hemoglobin
IPMN	Intraductal papillary mucinous neoplasm
MCN	Mucinous cystic neoplasm
MHRA	Medicine and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIDDK	National Institute for Diabetes and Digestive and Kidney Diseases
NIHR	National Institute for Health Research
PanIN3	Pancreatic intraepithelial neoplasia-3
SEER	Surveillance, Epidemiology, and End Results
UK	United Kingdom
US	United States
VAMP	Value Added Medical Products

Chapter 1

Introduction

1 Introduction

1.1 Pancreatic cancer

1.1.1 Terminology

Pancreatic cancer is defined as any malignant neoplasm of the pancreas.[1] The term is widely used synonymously with pancreatic ductal adenocarcinoma, which is by far the most common type of pancreatic malignancies.[1] In fact, up to 95% of pancreatic cancer cases represent pancreatic ductal adenocarcinomas.[2,3] They arise from the exocrine part of the pancreas, with 60% to 70% of the tumors being located in the head of the organ.[4] Approximately 10% of pancreatic ductal adenocarcinomas display a hereditary component, with the remainder occurring in the sporadic setting.[3,5]

1.1.2 Epidemiology

Pancreatic cancer is only the 12th most commonly diagnosed malignancy, but is the 7th most common cause of cancer-related death worldwide.[6] In 2020, 496,000 subjects were diagnosed with pancreatic cancer and nearly the same number of patients died from the disease.[7] Pancreatic cancer is 3- to 5-fold more common in high-income countries than in middle- or low-income countries.[7,8] The age-standardized incidence rate in Western Europe is 9 per 100,000 person-years.[8] Pancreatic cancer occurs slightly more often in men than in women[6] and peaks at ages 65-69 years for men and at ages 75-79 years for women.[8] Due the ageing of the world's population and the increases in the prevalence of smoking, obesity, and diabetes mellitus (equals in the following: diabetes, DM), all of which are risk factors for pancreatic cancer, it is expected that the number of pancreatic cancer cases will rise in the upcoming years.[9] In several countries, pancreatic cancer has become or is projected to become one of the leading causes of cancer-related death given the diverging trends in death rates for pancreatic cancer and other types of cancers.[6] For example, in the United States (US), pancreatic cancer has recently surpassed breast cancer to become the third most common cause of cancer-related death[10] and is estimated to surpass colorectal cancer in 2026.[11]

1.1.3 Survival

Pancreatic cancer has one of the lowest survival rates of all cancers.[12] Based on data from the Surveillance, Epidemiology, and End Results (SEER) Program assessed between 2011 and 2017, the 1-year relative survival for pancreatic cancer in the US is 36% and the 5-year relative survival is 11%.[13] Survival estimates are comparable across high-income countries. The age-standardized 5-year relative survival ranges from 14.6% in Australia to 7.9% in the United

Kingdom (UK).[14] Pancreatic cancer survival depends primarily on tumor stage at diagnosis. Based on SEER data, the 1-year relative survival decreases from 60% for patients diagnosed at a localized stage to 55% for patients diagnosed at a regional stage and further down to 20% for patients with metastatic disease.[13] The corresponding 5-year relative survival estimates are 42%, 14%, and 3%.[13]

1.1.4 Challenges of pancreatic cancer

The dismal prognosis of pancreatic cancer may be attributed to varying factors.[15] However, since the survival rate significantly decreases with increasing tumor size[16] and worsening tumor stage, late diagnosis is the main driver for poor survival rates and frequently prohibits timely implementation of effective treatments. In fact, in the vast majority of patients, pancreatic cancer is detected at a time when tumors have invaded major adjacent blood vessels or have spread to other organs and thus are considered unresectable.[17] Based on SEER data, 11% of pancreatic cancer patients are diagnosed at a localized stage, 30% at a regional stage, and 52% at a metastatic stage (7% unstaged).[13] As little as 20% of all pancreatic cancer patients qualify for surgery at the time of diagnosis.[3,18] The main reason for delayed detection of pancreatic cancer is that patients develop symptoms only late during the course of the disease.[17] Cancer-related symptoms precede the cancer diagnosis by a median duration of 2 months.[19] Besides, symptoms and signs caused by pancreatic tumors are mainly vague and unspecific and may thus be attributed to other medical conditions.[20] Symptoms and signs that have been reported by pancreatic cancer patients include abdominal pain, back pain, diarrhea, nausea, and jaundice.[4,20]

Improvements in survival may be seen if the diagnosis of pancreatic cancer is shifted from a late to an early stage of disease progression.[2] Thus, effective screening programs are eagerly awaited enabling disease detection at an early stage when patients are still free from subjective complaints.[3] Early detection is the key for an improved survival in pancreatic cancer.[17]

1.2 Screening for pancreatic cancer

1.2.1 General aspects of screening

Definition

In 1968, J. Wilson and G. Jungner published their landmark report on “the principles and practice of screening for disease”, in which they defined screening as “the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly”.[21]

Aims

The aims of screening for a disease or a pre-disease abnormality are

- to reduce the mortality from a disease (e.g. breast cancer screening).
- to reduce the morbidity from a disease (e.g. diabetic retinopathy screening).
- to reduce the incidence of a disease (e.g. colorectal cancer screening).
- to offer choice (e.g. antenatal screening).[22]

Through early detection of a disease/pre-disease abnormality, screening intends to ensure early treatment or medical intervention, which leads to improved disease outcome or disease prevention.[22]

Screening pathway

Screening is - strictly speaking - a multi-step pathway rather than only a test. Figure 1.2-1 describes the consecutive steps in a screening process.

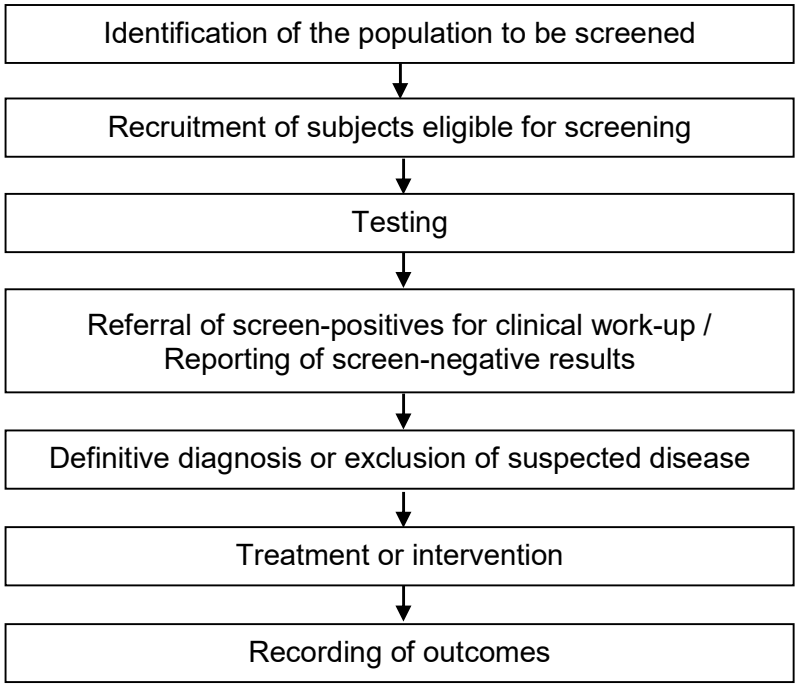

Figure 1.2-1. Steps in a screening process. Adapted from [22,23]

Screening test

A screening test is used to assess a subject's likelihood of having a condition.[24] Its result informs about whether or not presence of the condition must be suspected.[21] A screening test is typically performed in a large number of seemingly healthy people. Costs and harm associated with the test need to be sufficiently low to justify its application.[25] Thus, screening tests differ distinctly from diagnostic tests, which provide definite diagnosis and are typically

applied to symptomatic patients (or subjects with a positive screening test result). Higher costs and a higher risk of harm are often justified to establish a diagnosis.[25]

Outcomes of screening

Participants of a screening program may either profit from the screening intervention, have no benefits, or are even harmed by the screening.[26]

Subjects who benefit from screening are those who

- have the condition to be screened and whose prognosis is improved because of the early detection of it.
- have the condition to be screened and whose quality of life is improved because of the early detection and, as a result, the less aggressive treatment of it.
- do not have the condition to be screened and are reassured not to have it.[22,26]

Subjects who have no benefits from or may even be harmed by screening are those who

- are diagnosed with and treated for the condition to be screened but still have the same (good or poor) prognosis as they would have without screening.
- are diagnosed with and treated for the condition to be screened, which, however, would have never become clinically manifest during lifetime (overdiagnosis and overtreatment).
- obtain a false positive screening test result.
- obtain a false negative screening test result.[22,26]

Types of screening

There are different types of screening,[21,23] which include

- mass screening: a large-scale screening of whole population groups (e.g. newborn screening)
- selective / targeted screening: a screening restricted to subgroups considered to be at higher risk than the remaining population (e.g. testing for inherited *BRCA1* and *BRCA2* variants in individuals with affected relatives)

Screening vs. surveillance

Screening and surveillance are both health interventions aiming to detect a disease in its early stages. However, while screening is performed in subjects not seeking medical advice, surveillance is typically initiated upon clinical findings (e.g. surveillance for hepatocellular

carcinoma in patients with cirrhosis). Surveillance refers to a close, continuous, and long-term follow-up including repeated screening examinations.[21,27]

1.2.2 Feasibility of pancreatic cancer screening

In the absence of early, disease-specific symptoms, pancreatic cancer will only be detectable at an earlier stage, if apparently healthy people are examined for this disease, i.e. pancreatic cancer screening is performed. Hence, early detection of pancreatic cancer necessitates screening of asymptomatic subjects.[17]

In 1968, Wilson and Jungner developed the WHO principles of screening,[21] which remain relevant today. In the following, the most important principles will be discussed in the context of pancreatic cancer:

Aim

There should be a recognizable latent or early symptomatic phase.[21]

The goal of pancreatic cancer screening is to reduce the number of pancreatic cancer deaths and to identify cancer precursor lesions to reduce the burden of pancreatic cancer disease.[28] The pathological targets of pancreatic cancer screening are (a) precursor lesions including pancreatic intraepithelial neoplasia-3 (PanIN3) lesions and cystic lesions with high-grade dysplasia and (b) stage I pancreatic cancer.[28,29] The 5-year survival associated with stage IA and stage IB was found to be as high as 84% and 74%, respectively.[30] Recommendations from the American Gastroenterological Association and the International Cancer of the Pancreas Screening (CAPS) Consortium further suggest that the identification of localized pancreatic tumors that are resectable with negative margins should also be considered as a success of screening.[28,29]

Test/Modality

There should be a suitable test or examination.[21]

Magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) are currently the recommended screening modalities for the early detection of pancreatic cancer.[28,29] Computed tomography-based screening is reserved for subjects who cannot have MRI or EUS.[28] Pancreatic imaging with MRI has been reported to be particularly sensitive for the detection of cystic lesions, whereas pancreatic imaging with EUS was found to exhibit a particularly high sensitivity for the detection of small solid tumors.[29,31] Unlike MRI, EUS offers the possibility of

acquiring tissue samples for histological evaluation via fine-needle biopsy at the time of examination.[31] A major limitation of the currently applied screening modalities is their inability to detect PanIN lesions,[29] the most common type of precursor lesions of pancreatic cancer.[32] In addition, both imaging technologies are imperfect at distinguishing malignant cysts from benign cysts[15] and are associated with high costs.[33] Research efforts to improve the performance of applied screening modalities - by using artificial intelligence for example - are currently made.[34]

Therapy

There should be an accepted treatment for patients with recognized disease.[21]

Pancreatic resection in combination with chemotherapy is currently the only potentially curative therapy for pancreatic cancer.[35] Depending on the location of the tumor, different surgical techniques are applied. Pancreaticoduodenectomy (Whipple procedure), which typically involves removal of the head of the pancreas, most of the duodenum, the gallbladder, and part of the bile duct,[36] is the recommended operation if the tumor is located in the head of the pancreas. Distal pancreatectomy is the primary operation if the tumor occurs within the body or tail of the glandular organ.[35]

Type of screening

In 2019, the US Preventive Services Task Force reaffirmed its recommendation against pancreatic cancer screening in the general population, stating that the potential benefits of population-based screening do not outweigh the potential harms.[37] In fact, due to the low incidence of pancreatic cancer of 9 per 100,000 person-years,[8] pancreatic cancer screening would result in an unreasonably high number of false-positive cases when applied to the general population, while the yield of such screening (i.e. the number of cancer cases identified) is expected to be low.[37–39] Also, mass screening for pancreatic cancer would produce tremendous healthcare costs.[38] Thus, screening for pancreatic cancer needs to be targeted to selected high-risk groups.[28,29,40] Restriction of screening to subjects at increased risk of pancreatic cancer increases the probability of early disease detection and, consequently, improves screening performance.[38]

1.2.3 Target populations for pancreatic cancer screening

General definition

In the 2013 guidelines from the International CAPS Consortium, screening has been recommended for individuals with a lifetime risk for pancreatic cancer of >5% (5-fold increased risk).[41] However, when updating its recommendations in 2018, the International CAPS Consortium removed its general definition on whom to screen for pancreatic cancer from the guidelines and, instead, recommended screening for specified patient groups.[28]

At a summit of leading experts in the field of pancreatic cancer in 2020, which was held by the Kenner Family Research Fund and the American Pancreatic Association, it has been suggested that patient groups with a 3-year risk of having pancreatic cancer of 3% to 4% (25- to 50-fold increased risk) qualify for targeted pancreatic cancer screening.[34]

Established target populations

To date, pancreatic cancer screening is recommended for two different populations. These are: individuals with an inherited predisposition to pancreatic cancer and individuals with ≥ 1 pancreatic cyst harboring malignant potential.[15]

Individuals with an inherited predisposition to pancreatic cancer

Specific germline mutations usually present in the setting of genetic syndromes and familial clustering of pancreatic cancer are associated with high risk of developing pancreatic cancer. Table 1.2-1 presents the risks of pancreatic cancer in subjects with hereditary/familial predispositions. Specifically, pancreatic cancer screening is recommended for

- individuals with Peutz-Jeghers syndrome.
- individuals with hereditary pancreatitis.
- individuals with familial atypical multiple mole melanoma syndrome, Lynch syndrome, Li-Fraumeni syndrome, or hereditary breast and ovarian cancer syndrome (all hereditary cancer syndromes) + ≥ 1 affected first-degree relative.
- individuals with mutations in the *ATM* or *PALB2* gene + ≥ 1 affected first-degree relative.
- individuals with ≥ 2-3 affected genetically related relatives, of whom at least one is a first-degree relative to the person considered for screening.[28,29]

Table 1.2-1. Cumulative and relative risks of pancreatic cancer in subjects with hereditary/familial predispositions. Adapted from[42]

Predisposition	Identified genes	Cumulative risk of pancreatic cancer	Relative risk of pancreatic cancer
Peutz-Jeghers syndrome	*STK11/LKB1*	Up to 36% lifetime risk	132-fold
Familial pancreatitis syndrome	*PRSS1, SPINK1, PRSS2, CFTR*	Up to 53% at age 75 years	26- to 87-fold
Familial malignant melanoma syndrome	*P16/CDKN2A*	Up to 17% at age 75 years	13- to 46.6-fold
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	3.7% at age 70 years	8.6-fold
Hereditary breast-ovarian cancer syndrome	*BRCA1, BRCA2, PALB2*	1.5%-4.0% at age 70 years; more in *BRCA2*	*BRCA1*: 4- to 6-fold *BRCA2*: 3- to 22-fold *PALB2*: 6-fold
Familial pancreatic cancer	2 or more first-degree relatives with pancreatic cancer	3 or more first-degree relatives with pancreatic cancer: up to 16%-40%	3 or more first-degree relatives with pancreatic cancer: 32-fold
		2 first-degree relatives with pancreatic cancer: up to 12%	2 first-degree relatives with pancreatic cancer: 6-fold 1 first-degree relative with pancreatic cancer: 2- to 5-fold

Individuals with ≥ 1 pancreatic cyst harboring malignant potential

Current guidelines on the management of pancreatic cysts recommend screening - or rather surveillance - for surgically fit individuals

- with ≥ 1 cyst that is presumed to be either an intraductal papillary mucinous neoplasm (IPMN) or a mucinous cystic neoplasm (MCN) and does not show worrisome features (clinical or imaging) indicating an increased risk of malignancy.[43]
- with a surgically resected IPMN.[44,45]

For the two populations with a known increased risk of developing pancreatic cancer, screening - or more exactly surveillance - is performed at regular intervals using MRI or EUS. Individuals with an inherited predisposition to pancreatic cancer generally undergo surveillance examinations every 12 months,[28] while the interval for subjects with ≥ 1 suspicious pancreatic cyst ranges between 6 months and 2 years (depending on cyst size and appearance).[43]

Because 90% of all pancreatic cancers are sporadic[3,5] and cystic lesions are only discovered incidentally, when imaging examinations are performed,[45] further target populations for pancreatic cancer screening in addition to the previously established ones are needed.

Subjects with new-onset diabetes mellitus

Individuals with new-onset diabetes mellitus are the highest risk group currently known for sporadic pancreatic cancer. Subjects aged 50 years or older with new onset of diabetes have an approximately 8-fold increased risk of being diagnosed with pancreatic cancer in the 3 years after diabetes onset, when compared with the age-matched general population.[46] The 3-year incidence of pancreatic cancer in this group is around 1%.[46]

Temporal association between new-onset diabetes and pancreatic cancer

New onset of diabetes is a recognized manifestation of pancreatic cancer. It represents a paraneoplastic phenomenon, i.e. arises from tumor-derived substances rather than from tumor growth and subsequent glandular destruction.[47] Tumor-produced factors are considered to cause diabetes by triggering both insulin resistance and beta-cell dysfunction. Adrenomullin, a peptide, has been characterized as one potential mediator of beta-cell impairment. Despite these findings, the exact mechanism of pancreatic cancer-induced diabetes, including its mediators, is currently poorly understood.[47–49]

Pancreatic cancer-associated diabetes can precede the cancer diagnosis by less than 1 month up to several years. A study on the temporal association of new onset of diabetes with the diagnosis of pancreatic cancer found that diabetes was statistically significantly more frequent in cancer patients than in sex- and age-matched non-cancer patients starting from the 24 to 36-month time interval before the cancer diagnosis.[19]

Proportion of pancreatic cancer patients discovered by screening of patients with new onset of diabetes

The proportion of pancreatic cancer patients reported to have new-onset diabetes, i.e. develop diabetes within 24 months or 36 months before the cancer diagnosis, ranges between 20% and 59%, with the true proportion most likely lying somewhere in between.[50–53] No detailed data exist on how many of these patients will be detected from pancreatic cancer screening, i.e. have no cancer-specific symptoms at the time of diabetes onset. However, a prior cohort study, which followed up patients with new onset of diabetes for the occurrence of pancreatic cancer within 3 years, reported that 44% (n = 8 / 18) of the identified pancreatic cancer patients obtained their cancer diagnosis > 6 months after diabetes onset. These findings suggested

that somewhat less than half of the new-onset diabetic cancer patients may develop diabetes at a time when they are otherwise asymptomatic and, thus, may benefit from screening.[46]

The impact of pancreatic cancer screening on survival in patients with new-onset diabetes

There is first evidence that pancreatic cancer screening at the time of diabetes onset could lead to increased detection of early-stage tumors and, thus, to an improved prognosis. In a study on the characteristics of small carcinomas (≤ 2 cm in diameter), around 60% of the pancreatic tumors were associated with abnormal glucose tolerance test results, while approximately 44% of all small carcinomas belonged to stage I (and 43% to stage II).[54]

More robust evidence of an improved survival in patients diagnosed with pancreatic cancer at the time of diabetes onset has been provided by a recent study, which compared survival rates of patients who were asymptomatic and had new-onset diabetes (or exacerbation of existing diabetes) at the time of cancer diagnosis with those of patients who were diagnosed at a symptomatic stage. Findings of the study showed that asymptomatic diabetic patients were more likely than symptomatic patients to be diagnosed at stages 0-I (40% vs. 8%) and to undergo surgery (60% vs. 27%). The cumulative survival in the asymptomatic diabetic patients vs. symptomatic patients was 75% vs. 47% at 1 year and 32% vs. 15% at 3 years.[55]

It can be inferred that screening for asymptomatic patients with new-onset diabetes mellitus represents a potential clue for the early diagnosis of pancreatic cancer. However, the risk of asymptomatic *de novo* diabetes patients to develop pancreatic cancer is too low for justifying a screening approach. Therefore, further risk stratification is needed to enrich the population to be screened for pancreatic cancer.

Other populations at risk for development of sporadic pancreatic cancer

Apart from the high-risk group of subjects with new-onset diabetes mellitus, there are other conditions/diseases that are associated with low to moderate increases in risk for sporadic pancreatic cancer, such as smoking, heavy use of alcohol, obesity, history of pancreatitis, and long-standing diabetes.[56–58] Given the huge number of subjects with these risk factors, also here, further risk stratification is needed to enrich the population to be screened for pancreatic cancer.

1.3 Clinical Practice Research Datalink (CPRD) GOLD

CPRD GOLD is a UK-based primary care database that was established in 1987 under the name Value Added Medical Products (VAMP) Research Databank, then became the General Practice Research Database (GPRD) in 1993, before expanding to become the CPRD in

2012.[59] Today, the first European electronic health record database[60] is more precisely called CPRD GOLD to distinguish it from the 2017 launched database named CPRD Aurum.[61] CPRD GOLD is jointly supported by the Medicine and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR), as part of the Department of Health and Social Care.[59] With anonymized health information on more than 15 million patients, CPRD GOLD is one of the largest databases of longitudinal primary care data in the world.[59,60] Data are collected as part of routine care by some 700 general practices across the UK, which have agreed to contribute data to the database. CPRD GOLD contains information on patient demographics, symptoms, medical diagnoses (using “Read codes”), and drug prescriptions. Furthermore, information on lifestyle factors such as smoking, some clinical measures including body weight, and routine laboratory parameters such as blood glucose level are available in the database.[59] Patients enrolled in the CPRD GOLD are broadly representative of the UK general population with regard to age, sex, and ethnicity.[59] Moreover, CPRD GOLD data have repeatedly been demonstrated to be of high quality and validity.[62–64] Data from the CPRD GOLD have been the basis for over 2000 publications in peer-reviewed journals by now.[65] Studies using data from the CPRD GOLD require scientific approval from the Independent Scientific Advisory Committee (ISAC) for MHRA database research.[65]

Chapter 2

Aims of the thesis

2 Aims of the thesis

Screening for sporadic pancreatic cancer requires appropriate target populations.[40] Although different (high-)risk groups for sporadic pancreatic cancer have been identified, none carries a sufficiently high risk to justify imaging screening (surveillance).[34,37] To enrich known risk groups for pancreatic cancer, further risk stratification is needed.[34] Biomarkers specific for pancreatic cancer and/or easily accessible clinical or laboratory indicators of the disease could serve as enrichment tools.[34]

This thesis aimed to contribute to the understanding of whether body weight change and glycemic control can help to enrich the cohorts of new-onset diabetes subjects and long-standing diabetes subjects for pancreatic cancer, using data from the CPRD, a large primary care database from the UK.

New-onset diabetes mellitus population | In 2011, a small retrospective study demonstrated that, at the onset of diabetes, pancreatic cancer patients - on average - lost body weight, while non-cancer patients - on average - gained body weight.[66] Given these findings, loss in body weight has become a promising approach to distinguishing subjects with onset of pancreatic cancer-associated diabetes from subjects with onset of type 2 diabetes. Yet, it is currently not known how the magnitude of body weight loss interrelates with the likelihood of having developed pancreatic cancer. Also, no data exist on the association between body weight change and the timing of diabetes onset prior to the cancer diagnosis.

Type 2 diabetes develops over a long period of years,[67] whereas pancreatic cancer-associated diabetes was found to be of rapid onset.[68] Thus, absence of pre-diabetes (i.e. no elevated blood glucose levels) in the years before the onset of diabetes may indicate presence of pancreatic cancer. Study 3.1 aimed to evaluate the potential of weight loss and non-elevated blood glucose levels prior to the onset of diabetes as markers for pancreatic cancer.

Long-standing diabetes mellitus population | Disturbances in glucose metabolism manifest as new diabetes in previously normo-glycemic subjects and show up as exacerbation of existing diabetes in subjects already diagnosed with the disease. Hence, not only new-onset diabetes but also diabetes deterioration may be useful for advancing the early detection of pancreatic cancer. While blood glucose levels have been reported to increase in pancreatic cancer patients with pre-existing type 2 diabetes in the time prior to tumor detection,[68,69] detailed studies on the potential of diabetes deterioration as an early harbinger of pancreatic cancer are lacking. Thus, study 3.2 aimed to evaluate the association between glycemic control, body weight, and pancreatic cancer risk in patients with long-standing diabetes

(i.e. >2 years before the cancer diagnosis) in the 6 years before tumor detection. The objective of study 3.3 was to compare glycemic and body weight patterns of subjects with pancreatic cancer-associated deterioration of diabetes control with those of patients with type 2 diabetes progression.

Chapter 3

Pancreatic cancer project

3 Pancreatic cancer project

3.1 Weight change and blood glucose concentration as markers for pancreatic cancer in subjects with new-onset diabetes mellitus

A matched case-control study

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3.1.1 Abstract

Objectives: To evaluate the potential of blood glucose levels and weight change before the onset of diabetes as predictors of pancreatic cancer among subjects with new-onset diabetes, that is, cancer-related diabetes versus normal type 2 diabetes.

Methods: We conducted a case-control study among subjects with new diabetes in the United Kingdom-based Clinical Practice Research Datalink. Cases were pancreatic cancer subjects with diabetes for ≤2 years before the cancer diagnosis (i.e., cancer-related diabetes). Controls were cancer-free, type 2 diabetic subjects matched to cases on age, sex, and diabetes duration. We calculated adjusted odds ratios (aORs) for pancreatic cancer as a function of both weight change and blood glucose before the onset of diabetes.

Results: Weight loss of 10.0%-14.9% at diabetes onset was associated with an aOR for pancreatic cancer of 3.58 (95% CI 2.31-5.54), loss of ≥15.0%, with an aOR of 4.56 (95% CI 2.82-7.36), compared with stable weight. Blood glucose levels of ≤5.1 mmol/L or 5.2-5.6 mmol/L before diabetes onset were associated with an increased risk of a pancreatic cancer diagnosis, with aORs of 2.42 (95% CI 1.60-3.66) and 2.20 (95% CI 1.45-3.35), respectively, when compared with blood glucose levels ≥6.3 mmol/L within >2-3 years before cancer detection.

Conclusions: Weight loss as well as blood glucose levels in the normal range (and thus rapid development of hyperglycemia) before diabetes onset may be predictive of pancreatic cancer-related diabetes and may help target which subjects with new diabetes to refer for pancreatic cancer screening examinations.

3.1.2 Introduction

Pancreatic cancer recently surpassed breast cancer to become the third leading cause of cancer-related death in the United States.[10] It is projected to replace colorectal cancer as the second most common cause of cancer-related death by 2030.[70] The shifts are attributed to varying trends in both the number of new cases and the prognosis for the aforementioned types of cancer: While the incidence of pancreatic cancer has increased slightly over the past decade and the 5-year relative survival has remained virtually unchanged and below 10%,[10] the number of new colorectal cancer cases has markedly dropped,[10] and survival for both colorectal cancer[71] and breast cancer[72] has improved. Progress has been made in the fight against colorectal cancer and breast cancer as a result of treatment advances and the introduction of screening.[72,73]

Experts agree that targeted screening will also play a key role in reducing the number of deaths from pancreatic cancer.[74] Since disease-specific symptoms do not usually occur until late in the disease course, more than 80% of pancreatic cancer patients are currently not eligible for surgical resection at the time of diagnosis.[75] Surgery, however, is imperative for a favorable prognosis.[17] Pancreatic cancer screening could advance time of diagnosis, leading to the detection of tumors that are still potentially surgically resectable.[17] Given that pancreatic cancer is relatively rare, screening examinations should be limited to subjects at high risk for pancreatic cancer.[76] Today, new onset of diabetes mellitus (DM) after age 50 years is an established marker for non-inherited pancreatic cancer.[40] Yet, the number of subjects with new pancreatic cancer-related DM is low in relation to the number of cancer-free subjects with new type 2 DM.[46] Thus, identification of additional markers for pancreatic cancer in subjects with newly diagnosed DM could greatly advance the process of selecting candidates for screening examinations.[40]

One such marker could be weight loss. Studies have reported that more than 70% of pancreatic cancer patients with cancer-related DM (i.e., DM onset <36 months before cancer detection) exhibited weight loss around the time of the cancer diagnosis.[77,78] More important, Hart et al. found that pancreatic cancer subjects had already lost on average 2.1 ± 3.8 kg of their baseline body weight at the onset of DM, whereas non-cancer subjects had gained 1.4 ± 4.7 kg.[66] A recent study by Sharma et al. reported that 22% of pancreatic cancer patients studied had lost 2.0 to 3.9 kg at DM onset, 13% had weight loss of 4.0 to 5.9 kg, and an additional 36% had already lost 6.0 kg or more by the time of DM onset.[79] Other than weight loss, absence of high blood glucose levels in the years before the onset of DM could be indicative of increased risk of pancreatic cancer among subjects with newly diagnosed DM. Pancreatic cancer-related DM is considered to have a sudden onset,[80] implying that blood glucose levels rise over a short time. In contrast, subjects who develop type 2 DM exhibit

steady increases in blood glucose levels over several years before the DM diagnosis.[67] A case-control study in subjects with new-onset DM (i.e., DM onset ≤24 months before the index date) found that median blood glucose levels were lower in pancreatic cancer patients than in non-cancer patients during the years before the DM onset.[68]

More data on the associations of body weight change and blood glucose levels with pancreatic cancer in a new-onset DM population are needed to better understand the potential for these parameters to be effective indicators of the necessity for pancreatic cancer screening examinations. We therefore conducted a case-control study among subjects in the United Kingdom-based Clinical Practice Research Datalink (CPRD) who all had new-onset DM.

3.1.3 Methods

Study design and data source

We conducted a matched case-control study using data from the CPRD primary care database established in 1987. It encompasses anonymized records of around 13 million patients who are registered with some 700 participating general practices.[59] Validation of diagnostic data recording in the CPRD (using 'Read codes') has demonstrated high accuracy and comprehensiveness.[59,62,63] The CPRD has been used for numerous observational studies, including studies of pancreatic cancer[20,81,82] and body weight[83,84] or blood glucose levels.[85] The present study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research (protocol number 16_046) and has been made available to the journal editors.

Case and control identification

The study population consisted of subjects 35 to 89 years of age with (1) a first-time Read code for pancreatic cancer between January 2004 and December 2013 and (2) incident DM within 2 years before the cancer diagnosis,[86] referred to as 'new-onset DM' and considered to be cancer-related DM. We excluded potential cases who had a history of any other cancer (except non-melanoma skin cancer) at any time before the pancreatic cancer diagnosis date, subsequently referred to as the 'index date'. We additionally excluded subjects with less than 3 years of active history in the database before the index date to increase the likelihood of only evaluating cases with both incident pancreatic cancer and incident DM.

New-onset DM was defined as having either 'general practitioner (GP)-diagnosed DM' or 'biochemical DM' (DM supported by biochemistry but undiagnosed). Subjects were considered

to have GP-diagnosed DM if they met at least one of the following criteria within 2 years prior to the index date: (1) they had a first Read code for DM (type 1 DM, type 2 DM, or unspecified DM; without concurrent Read codes for other specific types of DM), or (2) they had a first prescription for an antidiabetic medication where at least one prescription was within 180 days before the index date. We used Read codes for type 1 DM to also detect cancer-related DM coded as type 1 DM due to the subject's rapid need for insulin[87] (presence of type 1 DM was considered unlikely because (1) DM onset was ≤2 years before the cancer diagnosis and (2) subjects were older than 30 years at DM diagnosis[88]). The date of GP-diagnosed DM onset was the date of the first Read code for DM or the date of the first antidiabetic prescription, whichever came first.

We also identified subjects with new-onset DM based on glycated hemoglobin (HbA_{1c}) and blood glucose levels since a DM code may not always have been recorded where pancreatic cancer was suspected. We classified these subjects as having biochemical DM. Subjects had biochemical DM if (1) their last recorded HbA_{1c} level within 180 days before the index date was 48 mmol/mol or greater, or (2) their last recorded blood glucose level within 180 days before the index date (fasting or unspecified provenance[89]) was 7 mmol/L or greater (or ≥11.1 mmol/L, when recorded on the same day as an oral glucose tolerance test was done and fasting status was not labeled). The record date of the elevated HbA_{1c} or blood glucose level was considered the date of onset of biochemical DM.

For each pancreatic cancer case, we selected up to 10 controls at random from among CPRD subjects who had new-onset DM (within 2 years of the index date of the matched case) and no diagnosis of pancreatic cancer. We applied the same inclusion and exclusion criteria to the controls as to the cases. We matched cases to controls on age (year of birth, ±3 years), sex, timing of DM onset (categorized as 0-0.5, >0.5-1, or >1-2 years before the index date), DM classification (GP-diagnosed DM or biochemical DM), calendar time (by using the same index date for controls as for cases), and number of years of history in the CPRD before the index date (±2 years).

Changes in body weight

For each case and control, we assessed the relative change in body weight from baseline (i.e., last weight record >3 years before the index date) to the time of DM onset (i.e., last weight record before DM onset, within 1 year) and from baseline to the index date (i.e., last weight record before the index date, within 1 year). Based on the existing literature,[77] we grouped relative weight change into 5 categories: weight gain, 3.1% or greater, stable weight, 3.0% or

less (absolute weight change was either positive or negative), weight loss, 3.1% to 9.9%, 10.0% to 14.9%, and 15.0% or greater.

Blood glucose levels

Using the approach described previously,[86] we retrieved blood glucose levels recorded before the onset of DM, that is, more than 2 years before the index date, for each case and control. We grouped blood glucose levels according to 5 distinct time intervals in which the tests were recorded: >2 to 3, >3 to 4, >4 to 5, >5 to 6, or >6 years prior to the index date. Then, within every time interval, we grouped blood glucose levels into 4 categories delineated by quartiles of blood glucose levels found among controls more than 6 years before the index date (category 1: ≤5.1 mmol/L, category 2: 5.2-5.6 mmol/L, category 3: 5.7-6.2 mmol/L, and category 4: ≥6.3 mmol/L).

Statistical analysis

We described subject characteristics of cases and controls based on recordings closest and prior to the index date. To evaluate the associations of weight change from baseline to DM onset and from baseline to the index date with pancreatic cancer, we applied multivariable conditional logistic regression. Using stable weight (i.e., ≤3.0% weight change) as the reference group, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) for the different categories of weight change. Subjects with missing data on body weight were categorized into an unknown weight change category. We further analyzed the association between blood glucose levels before the onset of DM and pancreatic cancer. Within the 5 defined time intervals more than 2 years before the index date, we compared the different blood glucose categories between cases and controls, with blood glucose of 6.3 mmol/L or greater (i.e., category 4) as the reference group. To complement findings of this analysis, we separately assessed glucose levels before DM onset among the subset of cases and controls who had recorded blood glucose levels in at least 2 time intervals before the onset of DM (more precisely within >2-3, >3-4, >4-5, and >5-6 years before the index date). Each subject was classified as having a *pattern* of either higher or lower blood glucose levels where higher levels belonged to categories 3 and 4 (5.7-6.2 mmol/L and ≥6.3 mmol/L, respectively). A case or control was considered to have a *pattern* of higher blood glucose levels, if the glucose level was higher in at least 2 of the 4 time intervals. Subjects were otherwise classified as having a *pattern* of lower blood glucose levels. We then calculated the OR for a diagnosis of pancreatic cancer associated with a *pattern* of lower when compared with the *pattern* of higher blood

glucose levels. In all analyses of glucose levels, we categorized subjects into an unknown category where data were missing on (the *pattern* of) blood glucose.

Based on the existing literature,[56,58] we adjusted all ORs for the following 4 covariates: smoking status (never, current, past, unknown; all before the index date), body mass index at baseline (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m², unknown; last value recorded >3 years before the index date), history of pancreatitis (yes, no; >2 years before the index date), and alcohol consumption (non-drinker, 1-14, ≥15 U/week, unknown; all before the index date). If a case or control had no information recorded on a particular covariate, we classified the subject as unknown for that variable.

In this study, information on blood glucose levels was missing in around 40% of both cases and controls and information on body weight was missing in at least one relevant study time window on around half of all subjects. To examine the potential for bias due to missing data, we repeated the analyses on weight change and blood glucose restricted to subjects with data available on the respective predictor variable as well as on the covariates (i.e., performed complete records analyses). To address errors in the assessment of DM status by including subjects with biochemical DM in our study, we performed sensitivity analyses restricted to subjects with GP-diagnosed DM. For a better understanding of the study results, we generated descriptive characteristics of cases and controls by type of weight change at DM onset (i.e., gain, stable, loss of 3.1%-9.9%, loss of ≥10.0%, or missing) and *pattern* of blood glucose levels (i.e., *pattern* of lower glucose levels, *pattern* of higher glucose levels, or missing). We used SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA) to conduct statistical analyses.

3.1.4 Results

Our study population included 588 pancreatic cancer cases and 5486 matched controls with new-onset DM, of which each approximately 60% had GP-diagnosed DM. Subject characteristics are summarized in Table 3.1-1. Cases were more likely to be current smokers and to have a history of pancreatitis (>2 years before the index date) than controls, but were less likely to be obese at baseline or to have cardiovascular disease.

Changes in body weight

Cases were more likely than controls to have lost weight at the onset of DM, with the risk increasing with increasing levels of weight loss (Table 3.1-2). Adjusted ORs (aORs) for pancreatic cancer were 1.57 (95% CI 1.13-2.19), 3.58 (95% CI 2.31-5.54), and 4.56

(95% CI 2.82-7.36) in subjects with weight loss of 3.1% to 9.9%, 10.0% to 14.9%, and 15.0% or greater, respectively, compared to subjects with stable weight. Results of the analysis restricted to subjects with GP-diagnosed DM were similar, with slightly lower aORs for weight loss of 3.1% to 9.9% (1.33 [95% CI 0.86-2.06]) and 10.0% to 14.9% (2.53 [95% CI 1.39-4.59]) and a higher aOR for loss of 15.0% or greater (6.70 [95% CI 3.64-12.34]). Data not shown.

The aORs for weight loss at the index date in relation to pancreatic cancer were higher than aORs for weight loss at DM onset (Table 3.1-2). Sensitivity analysis restricted to subjects with GP-diagnosed DM provided results similar to those of the primary analysis, except for the aOR in subjects with the highest level of weight loss, which was 21.79 (95% CI 13.63-34.84) (vs. 13.42 [95% CI 9.23-19.50] in primary analysis).

Blood glucose levels before the onset of DM

Lower blood glucose levels were associated with a greater risk of pancreatic cancer than higher blood glucose levels in the time intervals studied before the onset of DM (Table 3.1-3). In the >2 to 3 years before the index date, the aOR for blood glucose levels of 5.1 mmol/L or lower (lowest category) was 2.42 (95% CI 1.60-3.66) compared to blood glucose levels of 6.3 mmol/L or greater (highest category). The association between blood glucose levels of 5.1 mmol/L or lower and pancreatic cancer was broadly stable over the time period studied before the onset of DM, except for the somewhat lower aOR of 1.47 (95% CI 0.82-2.64) in the time interval for >5 to 6 years before the index date. Blood glucose levels of 5.2 to 5.6 mmol/L (category 2) were also associated with a generally increased risk of pancreatic cancer, though less strongly than were blood glucose levels of 5.1 mmol/L or lower (Table 3.1-3). For blood glucose levels of 5.7 to 6.2 mmol/L (category 3), we observed no material association with pancreatic cancer before the onset of DM. The analyses restricted to subjects with GP-diagnosed DM supported the positive association of lower glucose levels with pancreatic cancer, when compared to higher levels, with the ORs being generally somewhat lower.

In order to supplement findings of the aforementioned analysis, we separately assessed blood glucose levels in the subset of cases (N = 173) and controls (N = 2107) who had recorded levels for at least 2 defined time intervals before the onset of DM. We compared the *pattern* of lower glucose levels with the *pattern* of higher glucose levels and again found an increased risk of pancreatic cancer (aOR 1.98 [95% CI 1.43-2.74]) for subjects with lower glucose levels. The analysis restricted to subjects with GP-diagnosed DM yielded a comparable result.

We conducted additional analyses to better understand the study findings. We reanalyzed blood glucose levels and the data on weight change in complete records analyses. The obtained results closely matched the results of the primary analyses (with an additional

unknown category), except that the confidence intervals were wider due to smaller patient numbers. Data not shown. Table 3.1-4 provides subject characteristics by type of weight change at DM onset. Cases and controls with weight loss of 3.1% to 9.9% had DM, on average, for 5.9 (standard deviation [SD] 6.8) months and 6.5 (SD 6.3) months, respectively, before the index date. In contrast, subjects, cases in particular, who exhibited weight loss of 10.0% or greater at DM onset, had DM, on average, for a shorter time before the index date (i.e., 3.7 [SD 4.7] months in cases and 5.3 [SD 5.7] months in controls). Table 3.1-5 shows subject characteristics by *pattern* of blood glucose levels.

Table 3.1-1. Descriptive characteristics of pancreatic cancer cases and matched controls with new onset diabetes mellitus

	Cases (N = 588)[a], n (%)	Controls (N = 5486)[a], n (%)	OR crude (95% CI)
Sex			
Male	291 (49.5)	2698 (49.2)	NA
Female	297 (50.5)	2788 (50.8)	NA
Age at the index date, years			
<50	11 (1.9)	56 (1.0)	NA
50-59	59 (10.0)	559 (10.2)	NA
60-69	181 (30.8)	1713 (31.2)	NA
70-79	210 (35.7)	2019 (36.8)	NA
≥80	127 (21.6)	1139 (20.8)	NA
Type of diabetes			
Biochemical diabetes	250 (42.5)	2275 (41.5)	NA
GP-diagnosed diabetes	338 (57.5)	3211 (58.5)	NA
Diabetes duration, years			
0-0.5	419 (71.3)	3856 (70.3)	NA
>0.5-1	79 (13.4)	739 (13.5)	NA
>1-2	90 (15.3)	891 (16.2)	NA
Smoking status			
Never	229 (39.0)	2197 (40.1)	1 (Reference)
Current	105 (17.9)	643 (11.7)	1.61 (1.25-2.08)
Past	250 (42.5)	2596 (47.3)	0.93 (0.77-1.13)
Unknown	X	50 (0.9)	X
Alcohol consumption, U/week			
Non-drinker	297 (50.5)	2865 (52.2)	1 (Reference)
1-14	182 (31.0)	1751 (31.9)	1.00 (0.82-1.22)
≥15	63 (10.7)	537 (9.8)	1.12 (0.83-1.52)
Unknown	46 (7.8)	333 (6.1)	1.34 (0.96-1.87)
BMI at baseline[b], kg/m²			
<18.5	6 (1.0)	30 (0.6)	1.43 (0.58-3.51)
18.5-24.9	119 (20.2)	820 (15.0)	1 (Reference)
25.0-29.9	208 (35.4)	1970 (35.9)	0.72 (0.57-0.92)
≥30.0	169 (28.7)	2022 (36.9)	0.56 (0.43-0.72)
Unknown	86 (14.6)	644 (11.7)	0.90 (0.67-1.22)
Comorbidities			
Previous pancreatitis (>2 years before the index date)	14 (2.4)	60 (1.1)	2.27 (1.26-4.09)
Hypertension	300 (51.0)	3374 (61.5)	0.65 (0.55-0.77)
Ischemic heart disease	108 (18.4)	1304 (23.8)	0.72 (0.58-0.90)
Stroke / TIA	46 (7.8)	599 (10.9)	0.68 (0.49-0.93)
Dyslipidemia	126 (21.4)	1392 (25.4)	0.80 (0.65-0.99)
Statins, number of prescriptions			

None	301 (51.2)	2074 (37.8)	1 (Reference)
1-24	139 (23.6)	1776 (32.4)	0.53 (0.42-0.66)
≥25	148 (25.2)	1636 (29.8)	0.61 (0.49-0.76)
Antidiabetic medication			
None	343 (58.3)	4081 (74.4)	1 (Reference)
Oral	183 (31.1)	1359 (24.8)	2.29 (1.81-2.90)
Insulin	23 (3.9)	25 (0.5)	16.81 (8.86-31.92)
Oral and insulin combined	39 (6.6)	21 (0.4)	31.02 (17.62-54.61)

OR odds ratio, *CI* confidence interval, *NA* not applicable, *GP* general practitioner, *X* cell contains fewer than 5 subjects (owing to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 subjects), *BMI* body mass index, *TIA* transient ischemic attack

[a] Because of rounding, percentages may not total 100.

[b] Defined as latest recorded BMI more than 3 years before the index date.

Table 3.1-2. Odds ratios for pancreatic cancer associated with body weight changes in subjects with new-onset diabetes mellitus at both the onset of diabetes mellitus and the index date

	Cases (N = 588)[a], n (%)	Controls (N = 5486)[a], n (%)	OR crude (95% CI)	OR adjusted[b] (95% CI)
Body weight change at the onset of diabetes, %				
Weight gain: ≥3.1	60 (10.2)	1082 (19.7)	0.60 (0.43-0.84)	0.57 (0.41-0.80)
Stable weight: ≤3.0	91 (15.5)	989 (18.0)	1 (Reference)	1 (Reference)
Weight loss:				
3.1-9.9	71 (12.1)	495 (9.0)	1.58 (1.14-2.20)	1.57 (1.13-2.19)
10.0-14.9	37 (6.3)	112 (2.0)	3.62 (2.35-5.57)	3.58 (2.31-5.54)
≥15.0	32 (5.4)	73 (1.3)	4.94 (3.08-7.92)	4.56 (2.82-7.36)
Unknown	297 (50.5)	2735 (49.9)	1.17 (0.92-1.51)	1.06 (0.82-1.38)
Body weight change at the index date, %				
Weight gain: ≥3.1	48 (8.2)	1211 (22.1)	0.70 (0.48-1.03)	0.67 (0.45-0.98)
Stable weight: ≤3.0	64 (10.9)	1177 (21.5)	1 (Reference)	1 (Reference)
Weight loss:				
3.1-9.9	93 (15.8)	829 (15.1)	2.14 (1.53-2.99)	2.16 (1.55-3.03)
10.0-14.9	77 (13.1)	244 (4.5)	6.42 (4.45-9.27)	6.32 (4.36-9.16)
≥15.0	97 (16.5)	142 (2.6)	13.59 (9.39-19.67)	13.42 (9.23-19.50)
Unknown	209 (35.5)	1883 (34.3)	2.00 (1.48-2.70)	1.67 (1.21-2.32)

OR odds ratio, *CI* confidence interval

[a] Because of rounding, percentages may not total 100.

[b] Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption.

Table 3.1-3. Odds ratios for pancreatic cancer associated with blood glucose levels before the onset of diabetes in subjects with new-onset diabetes mellitus by time from glucose recording to index date

	Time interval before the index date				
	>6 years	>5 to 6 years	>4 to 5 years	>3 to 4 years	>2 to 3 years
Blood glucose category[a]					
1					
cases/controls, n	82/515	30/315	46/323	59/349	48/321
aOR[b] (95% CI)	3.14 (1.92-5.13)	1.47 (0.82-2.64)	2.33 (1.44-3.79)	3.12 (2.02-4.83)	2.42 (1.60-3.66)
2					
cases/controls, n	42/479	37/314	43/384	42/372	44/335
aOR[b] (95% CI)	1.77 (1.04-3.02)	1.94 (1.10-3.40)	1.90 (1.16-3.11)	2.02 (1.27-3.21)	2.20 (1.45-3.35)
3					
cases/controls, n	42/472	28/354	25/466	35/481	57/563
aOR[b] (95% CI)	1.73 (1.01-2.95)	1.32 (0.74-2.39)	0.88 (0.51-1.52)	1.30 (0.81-2.10)	1.67 (1.13-2.45)
4					
cases/controls, n	22/437	21/356	30/489	38/695	56/957
aOR[b] (95% CI)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Missing values					
cases/controls, n	400/3583	472/4147	444/3824	414/3589	383/3310
aOR[b] (95% CI)	2.10 (1.34-3.30)	1.81 (1.15-2.87)	1.85 (1.25-2.73)	2.03 (1.43-2.87)	1.86 (1.38-2.50)

aOR adjusted odds ratio, *CI* confidence interval

[a] Category 1: 5.1 mmol/L or lower, category 2: 5.2-5.6 mmol/L, category 3: 5.7-6.2 mmol/L, and category 4: 6.3 mmol/L or greater.

[b] Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption.

Table 3.1-4. Descriptive characteristics of pancreatic cancer cases and matched controls with new onset diabetes mellitus, stratified by type of weight change at diabetes onset

	Cases (N = 588)					Controls (N = 5486)				
Type of weight change at diabetes onset	Missing	Weight gain	Stable weight	Weight loss of 3.1%-9.9%	Weight loss of ≥10.0%	Missing	Weight gain	Stable weight	Weight loss of 3.1%-9.9%	Weight loss of ≥10.0%
	[N = 297]	[N = 60]	[N = 91]	[N = 71]	[N = 69]	[N = 2735]	[N = 1082]	[N = 989]	[N = 495]	[N = 185]
Characteristic										
GP-diagnosed diabetes[a]	162 (54.5)	39 (65.0)	59 (64.8)	38 (53.5)	40 (58.0)	1499 (54.8)	692 (64.0)	617 (62.4)	294 (59.4)	109 (58.9)
Number of GP encounters/year[b,c]	14.1 (9.8)	17.1 (8.2)	18.5 (8.6)	19.6 (12.3)	14.9 (8.1)	13.4 (9.3)	15.7 (10.0)	15.4 (10.1)	15.0 (9.9)	17.8 (12.6)
Male[a]	143 (48.2)	28 (46.7)	45 (49.5)	40 (56.3)	35 (50.7)	1343 (49.1)	532 (49.2)	495 (50.1)	261 (52.7)	67 (36.2)
Age at the index date[b], years	71.1 (10.5)	67.5 (9.2)	71.5 (8.1)	72.6 (8.9)	71.0 (9.8)	71.6 (9.5)	68.6 (8.9)	70.7 (8.7)	72.4 (9.0)	73.4 (9.0)
BMI at baseline[b,d], kg/m²	28.2 (5.4)	29.6 (5.4)	28.0 (5.2)	28.7 (4.8)	29.0 (5.8)	29.3 (5.3)	29.6 (5.5)	30.3 (5.4)	30.0 (5.4)	29.7 (5.9)
Comorbidities[a]										
Hypertension	130 (43.8)	37 (61.7)	52 (57.1)	46 (64.8)	35 (50.7)	1581 (57.8)	696 (64.3)	664 (67.1)	324 (65.5)	109 (58.9)
Ischemic heart disease	39 (13.1)	14 (23.3)	24 (26.4)	21 (29.6)	10 (14.5)	517 (18.9)	306 (28.3)	288 (29.1)	146 (29.5)	47 (25.4)
Stroke / TIA	21 (7.1)	X	7 (7.7)	7 (9.9)	8 (11.6)	309 (11.3)	115 (10.6)	96 (9.7)	55 (11.1)	24 (13.0)
Dyslipidemia	55 (18.5)	19 (31.7)	19 (20.9)	21 (29.6)	12 (17.4)	585 (21.4)	315 (29.1)	306 (30.9)	145 (29.3)	41 (22.2)
Gout	15 (5.1)	7 (11.7)	8 (8.8)	9 (12.7)	5 (7.3)	287 (10.5)	127 (11.7)	112 (11.3)	57 (11.5)	16 (8.7)
Depression	56 (18.9)	17 (28.3)	20 (22.0)	13 (18.3)	15 (21.7)	502 (18.4)	241 (22.3)	200 (20.2)	99 (20.0)	49 (26.5)
Osteoporosis	14 (4.7)	X	5 (5.5)	X	X	121 (4.4)	49 (4.5)	35 (3.5)	27 (5.5)	21 (11.4)
COPD	16 (5.4)	5 (8.3)	8 (8.8)	8 (11.3)	8 (11.6)	144 (5.3)	78 (7.2)	63 (6.4)	49 (9.9)	29 (15.7)
Time of diabetes onset before the index date[b,e], months	4.8 (5.9)	7.2 (7.7)	5.9 (6.2)	5.9 (6.8)	3.7 (4.7)	5.9 (6.0)	6.2 (6.0)	6.5 (6.3)	6.5 (6.3)	5.3 (5.7)
Time between record date of 'weight at diabetes onset' and the index date[b,f], months	NA	11.0 (8.0)	9.2 (7.0)	8.4 (7.4)	4.9 (5.7)	NA	8.8 (6.5)	9.5 (7.1)	9.3 (6.7)	7.6 (6.2)

GP general practitioner, *BMI* body mass index, *TIA* transient ischemic attack, *X* cell contains fewer than 5 subjects (owing to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 subjects), *COPD* chronic obstructive pulmonary disease, *NA* not applicable

[a] Data presented as number (%).

[b] Data presented as mean (standard deviation).

[c] Based on the diagnostic recording within 3 years before the index date.

[d] Defined as latest recorded BMI more than 3 years before the index date.

[e] Corresponding numbers among the subset of subjects with GP-diagnosed diabetes: cases: 7.6 (6.7), 10.4 (7.9), 8.2 (6.6), 9.9 (7.2), 5.4 (5.5) months, controls: 8.7 (6.8), 8.2 (6.5), 8.9 (6.9), 9.2 (6.9), 7.3 (6.5) months.
[f] Corresponding numbers among the subset of subjects with GP diagnosed diabetes: cases: 13.6 (8.5), 11.1 (7.4), 12.1 (7.9), 6.8 (6.6) months, controls: 10.5 (6.9), 11.3 (7.7), 11.3 (7.2), 8.9 (7.0) months.

Table 3.1-5. Descriptive characteristics of pancreatic cancer cases and matched controls with new onset diabetes mellitus, stratified by *pattern* of blood glucose levels before the diabetes onset

	Cases (N = 588)				**Controls (N = 5486)**			
Pattern of blood glucose levels	Missing [N = 415]		*Pattern* of lower blood glucose levels [N = 107]	*Pattern* of higher blood glucose levels [N = 66]	Missing [N = 3379]		*Pattern* of lower blood glucose levels [N = 933]	*Pattern* of higher blood glucose levels [N = 1174]
	No blood glucose levels [N = 241]	Blood glucose level in a single time interval [N = 174]			No blood glucose levels [N = 1998]	Blood glucose level in a single time interval [N = 1381]		
Characteristic								
GP-diagnosed diabetes[a]	134 (55.6)	93 (53.4)	56 (52.3)	55 (83.3)	1242 (62.2)	791 (57.3)	434 (46.5)	744 (63.4)
Time of diabetes onset before the index date[b,c], months	4.5 (5.7)	5.0 (6.4)	4.2 (5.3)	9.9 (6.8)	6.2 (6.2)	5.9 (6.1)	5.1 (5.4)	6.9 (6.5)
Number of GP visits/year[b,d]	9.0 (6.4)	12.9 (7.1)	15.9 (7.7)	17.3 (9.9)	8.5 (6.0)	11.9 (8.1)	15.5 (8.7)	14.5 (8.5)
Male[a]	120 (49.8)	90 (51.7)	51 (47.7)	30 (45.5)	1045 (52.3)	674 (48.8)	399 (42.8)	580 (49.4)
Age at the index date[b], years	69.5 (10.0)	71.9 (9.9)	72.0 (9.2)	72.3 (9.2)	69.9 (9.4)	70.6 (9.5)	72.3 (9.1)	72.3 (8.5)
BMI at baseline[b,e], kg/m²	27.3 (5.3)	28.6 (4.9)	29.1 (5.0)	30.6 (6.4)	29.2 (5.2)	29.7 (5.4)	29.9 (5.8)	30.2 (5.5)
Comorbidities[a]								
Hypertension	86 (35.7)	94 (54.0)	70 (65.4)	50 (75.8)	1031 (51.6)	830 (60.1)	658 (70.5)	855 (72.8)
Ischemic heart disease	22 (9.1)	29 (16.7)	35 (32.7)	22 (33.3)	339 (17.0)	294 (21.3)	302 (32.4)	369 (31.4)
Stroke / TIA	12 (5.0)	15 (8.6)	9 (8.4)	10 (15.2)	174 (8.7)	138 (10.0)	143 (15.3)	144 (12.3)
Dyslipidemia	30 (12.5)	33 (19.0)	41 (38.3)	22 (33.3)	372 (18.6)	311 (22.5)	326 (34.9)	383 (32.6)
Gout	15 (6.2)	13 (7.5)	10 (9.4)	6 (9.1)	179 (9.0)	139 (10.1)	122 (13.1)	159 (13.5)
Depression	45 (18.7)	36 (20.7)	22 (20.6)	18 (27.3)	315 (15.8)	282 (20.4)	223 (23.9)	271 (23.1)
Osteoporosis	11 (4.6)	7 (4.0)	7 (6.5)	X	60 (3.0)	69 (5.0)	69 (7.4)	55 (4.7)

COPD	14 (5.8)	14 (8.1)	12 (11.2)	5 (7.6)	108 (5.4)	97 (7.0)	82 (8.8)	76 (6.5)

GP general practitioner, *BMI* body mass index, *TIA* transient ischemic attack, *X* cell contains fewer than 5 subjects (owing to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 subjects), *COPD* chronic obstructive pulmonary disease

[a] Data presented as number (%).

[b] Data presented as mean (standard deviation).

[c] Corresponding numbers among the subset of subjects with GP-diagnosed diabetes: cases: 7.0 (6.6), 8.2 (7.4), 6.7 (6.2), 11.6 (6.1) months, controls: 8.5 (6.7), 8.5 (6.8), 8.1 (6.5), 9.4 (6.9) months.

[d] Based on the diagnostic recording within 6 years before the index date.

[e] Defined as latest recorded BMI more than 3 years before the index date.

3.1.5 Discussion

In this case-control study, relative weight loss as well as normal blood glucose levels (and thus rapid development of hyperglycemia) before the onset of DM were found to be potential markers of pancreatic cancer among subjects with new-onset DM, that is, potential indicators of pancreatic cancer-related DM (vs. normal type 2 DM).

We observed that twice as many pancreatic cancer cases as controls had lost weight at the time of DM onset. Our findings corroborate those of the study by Hart et al., which described a 2:1 ratio of pancreatic cancer patients to non-cancer patients with weight loss at the onset of DM.[66] The proportions of pancreatic cancer and non-cancer subjects with weight loss before the onset of DM were, however, lower in our study (24% vs. 12%) than in the Hart et al. study (59% vs. 30%).[66] This is likely explained by our definition of weight loss (i.e., >3.0% weight change) and by the proportion of subjects who had missing weight information.

In the Sharma et al. study, around 51% of the pancreatic cancer patients with weight loss at the onset of DM (i.e., ≤ -2 kg weight change) had lost 6 kg or more of their baseline body weight, whereas only 44% of non-cancer patients had weight loss of a similar magnitude among those with weight loss at the time of DM onset.[79] Our results were similar to these findings and showed that higher weight loss at the onset of DM was a stronger marker for a subsequent diagnosis of pancreatic cancer than lower weight loss; aORs for loss of 10.0% to 14.9% and 15.0% or greater were 3.58 (95% CI 2.31-5.54) and 4.56 (95% CI 2.82-7.36), respectively. However, cancer subjects with weight loss of 10.0% or greater at DM onset developed the DM within 6 months before the cancer diagnosis on average, and at a time when other clinical signs, such as abdominal or back pain, typically occur.[19] Hence, using serious weight loss at DM onset as an indicator of the need for pancreatic cancer screening may be too late to help the cancer prognosis.

Among the cancer subjects with lower weight loss of 3.1% to 9.9% at DM onset, a relevant number of subjects seemed to develop DM more than 6 months prior to the cancer diagnosis, and thus at a time when tumors are reported to be still resectable.[75] Given that the association between lower weight loss at DM onset and pancreatic cancer was weak (aOR, 1.57 [95% CI 1.13-2.19]), minor weight loss may be primarily useful as a marker for pancreatic cancer among subjects with new-onset DM, if applied in combination with additional criteria. Another possible way to increase the predictive power of small amounts of weight loss at DM onset could be to evaluate weight change at the onset of DM as part of the overall temporal pattern of body weight change. This is supported by our finding that there were more pancreatic cancer subjects with serious weight loss at the time of cancer diagnosis than at DM onset, resulting in aORs of 6.32 (95% CI 4.36-9.16) and 13.42 (95% CI 9.23-19.50) for weight loss of

10.0% to 14.9% and 15.0% or greater, respectively, at the index date. Yet, it remains to be demonstrated that weight loss progresses continuously after DM onset rather than increasing abruptly before the cancer diagnosis. Weight loss at DM onset is considered to be a paraneoplastic feature of pancreatic cancer,[47] whereas reductions in body weight observed at the time of cancer detection could also mainly be the result of cachexia, which does not typically occur until 2 months before the cancer diagnosis and which leads to a rapid decline in body weight.[47]

One important goal of this study was to evaluate whether the blood glucose concentration before DM onset may be predictive of pancreatic cancer-related DM, that is, a marker of pancreatic cancer among subjects with new-onset DM. Pancreatic cancer-related DM is a well-known paraneoplastic phenomenon[47] where glucose levels rise abruptly.[80] Type 2 DM, conversely, usually occurs after many years of increasing blood glucose levels.[67] Thus, normal glucose levels in the years before DM onset might be useful to identify subjects at increased risk of pancreatic cancer-related DM. In fact, we observed that cancer subjects were more likely than non-cancer subjects to exhibit normal blood glucose levels in the years before DM onset (aORs for glucose levels of ≤5.1 mmol/L were 2.42 [95% CI 1.60-3.66] and 3.12 [95% CI 2.02-4.83] within >2-3 and >3-4 years before the index date, respectively). Similarly, we found that subjects with a *pattern* of lower blood glucose levels before the onset of DM were at greater risk of having pancreatic cancer than subjects with a *pattern* of higher blood glucose levels. Hence, absence of prediabetes in the years before DM onset may be predictive of cancer-related DM. Existing literature reports varying findings on the association between blood glucose levels prior to DM onset and pancreatic cancer. A previously published study found no difference in the mean blood glucose levels of pancreatic cancer and non-cancer patients before the onset of DM.[66] However, another case-control study found lower median blood glucose levels in pancreatic cancer patients than in non-cancer patients during the years preceding the onset of DM.[68] Consistent with this finding, a very recent study reported blood glucose to be below 5.6 mmol/L in 19% of pancreatic cancer patients but in only 5% of non-cancer patients about 1 year before DM onset.[79]

Among the cases with a *pattern* of lower glucose levels before DM onset, occurrence of DM preceded the pancreatic cancer diagnosis by only 4.2 (SD 5.3) months on average (GP-diagnosed DM population: 6.7 [SD 6.2] months), whereas among those with a *pattern* of higher glucose levels, the onset of DM preceded cancer detection by 9.9 (SD 6.8) months on average (GP-diagnosed DM population: 11.6 [SD 6.1] months). It would mean that several of the pancreatic cancer subjects who are likely to benefit most from screening examinations around the time of DM onset (develop DM earliest prior to cancer detection) will be missed, when applying normal blood glucose concentration prior to DM onset as a marker for

pancreatic cancer. However, as we retrieved blood glucose records in all subjects from more than 2 years before the index date, we might have observed elevated glucose levels in the subjects with DM onset more distant from the cancer diagnosis date only because the tumor had already affected glucose metabolism. Yet, it could also be that the subjects with DM onset early in the course of cancer are subjects predisposed to type 2 DM who have therefore elevated glucose levels before the onset of DM. A previous study of Pannala et al. has hypothesized something similar when proposing that subjects susceptible to type 2 DM are more likely to develop DM when pancreatic cancer occurs than those without risk factors for DM.[68]

In our study, around 40% of cases and controls did not have glucose levels in their records during the time period studied, and around half of all subjects did not have data on weight in at least one relevant time window. This could have led to biased results on the associations between weight change, blood glucose, and pancreatic cancer. However, complete records analyses yielded similar results as our primary analyses, where we categorized subjects with missing data into an unknown category. A logistic regression analysis restricted to complete records provides unbiased results, unless missing data jointly depend on the predictor variable studied (weight change/blood glucose) and the case-control status.[90,91] Whether this missing scenario is given in a study cannot be tested.[90] Yet, to then detect erroneously a positive association between weight loss and pancreatic cancer, it seems necessary, given our considerations, that controls with missing information on weight were either (1) more likely to lack data on weight loss than cases with missing information, or (2) more likely to lack data on weight gain, while corresponding cases were more likely to lack data on stable weight. With regard to blood glucose, we would assume that cases with missing values had to be more likely to lack a *pattern* of higher blood glucose levels than the corresponding controls. We could not see that the latter should be the case given the descriptive characteristics of cases and controls with no data on the glucose *pattern* and the characteristics of cases and controls with a *pattern* of lower or higher glucose levels. The table showing characteristics of cases and controls by type of weight change was somewhat more complex, but it did not provide evidence for an erroneously observed association between weight loss and pancreatic cancer. In addition, as stated above, there is a plausible biological explanation (i.e., paraneoplastic phenomenon) for the observed associations and consistency between our results and those of previous studies.

This study has some other limitations. First, the diagnostic Read codes for pancreatic cancer did not allow us to distinguish between pancreatic ductal adenocarcinomas and other types of pancreatic tumors. However, ductal adenocarcinomas account for about 80% of all pancreatic cancers.[92] As such, the impact of other types of pancreatic tumors on our findings is likely to

be minimal. Second, because we defined new-onset DM not only based on record entries for DM but also on laboratory values, we may have included subjects in our study that were not true DM subjects. However, sensitivity analyses restricted to subjects with GP-diagnosed DM provided results similar to those of the full analyses. Third, we did not stratify our regression analyses on time of DM occurrence given the small number of subjects available. Yet, we described time of DM onset according to type of weight change or *pattern* of blood glucose levels, thereby providing some information on the potential role of DM onset time in the associations between weight change, blood glucose, and pancreatic cancer. Fourth, we cannot rule out the possibility that some blood glucose levels included in the analyses had been measured in the non-fasting state, in particular because the provenance of most blood glucose levels was unspecified. However, a study on the recording of blood glucose in primary care in the United Kingdom showed that the distribution of glucose levels with unknown provenance resembled the distribution of fasting glucose values.[89] More importantly, we observed in our previous study on the CPRD that analyses of blood glucose levels led to the same conclusions as analyses of HbA_{1c} levels.[86]

In conclusion, this study provides evidence that weight loss at DM onset is predictive of pancreatic cancer-related DM and thus serves as a marker for pancreatic cancer among subjects with new-onset DM. It supports British Referral Guidelines that recommend pancreatic cancer diagnostic workup in subjects with new-onset DM accompanied by weight loss.[93] Having a small amount of weight loss at DM onset might be a weaker marker for pancreatic cancer than having serious weight loss. However, it is the cancer patient with minor weight loss at DM onset who may particularly benefit from screening examinations around the time of DM occurrence (DM onset more distant from cancer detection). Thus, pancreatic cancer risk prediction models which are based not only on the amount of weight loss but also on additional criteria[79,94] may be particularly useful in subjects with new-onset DM. Having normal blood glucose levels in the years before DM onset (and thus showing rapid development of hyperglycemia) could be one of the additional indicators of pancreatic cancer-related DM. While our results provide clinically important evidence, further studies need to be conducted to evaluate their reliability, particularly in light of the amount of data missing in the current analyses. Ongoing new-onset DM cohorts[95,96] will offer the opportunity to perform such future studies on large and very complete datasets.

3.2 The potential of glycemic control and body weight change as early markers for pancreatic cancer in patients with long-standing diabetes mellitus

A case-control study

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3.2.1 Abstract

Objectives: The aim of this study was to characterize the role of glycemic control and weight change as markers for pancreatic cancer (PaC) in patients with long-standing diabetes.

Methods: We conducted case-control analyses in patients with long-standing diabetes (>2 years) in the UK-based Clinical Practice Research Datalink. Cases were patients with PaC matched to controls on variables including age, sex, and diabetes duration. We compared glycated hemoglobin (HbA_{1c}) levels, blood glucose levels, and weight change before cancer detection (matched date) between cases and control subjects to assess associations between the potential markers and PaC.

Results: Cases were more likely than control subjects to have high HbA_{1c} levels. The adjusted odds ratio (aOR) was 4.94 (95% confidence interval [CI], 3.52-6.94) for HbA_{1c} of 64.0 mmol/mol or greater compared with HbA_{1c} of 47.5 mmol/mol or less within 6 months before cancer detection, and within >1 to 2 years, 2.66 (95% CI, 2.00-3.54). Weight loss was also more common in cases, with an aOR of 15.40 (95% CI, 10.65-22.26) for loss of 15.0% body weight or greater compared with stable weight. The aOR for patients with both weight loss 15.0% or greater and high HbA_{1c} at 2 years or less before diagnosis was 60.97 (95% CI, 35.87-103.65), compared with patients with neither.

Conclusions: Poor glycemic control and weight loss, particularly in combination, may be useful early markers for PaC in patients with long-standing diabetes.

3.2.2 Introduction

Approximately 50% of all pancreatic cancers are diagnosed after metastases have occurred, and another 30% are diagnosed, after regional lymph nodes have been affected. Based on the 5-year survival rate for comparable noncancer patients, the 5-year relative survival for these patients is 2.7% and 11.5%, respectively. However, among patients whose cancer is detected before lymph node involvement, the 5-year relative survival is 31.5%.[97] Thus, early detection is critical for increased life expectancy in pancreatic cancer patients and novel means to detect pancreatic cancer before the tumor spreads and while it can still be removed, are needed.[75] Because early and specific clinical symptoms are uncommon, targeted pancreatic cancer screening is required.[76] In addition, given that pancreatic cancer is so rare, screening must encompass 2 steps to be feasible and cost-effective: (1) it must identify subjects at high risk of occult pancreatic cancer and (2) it must confirm or rule out the suspected diagnosis in preselected subjects.[74] Today, the only established marker for occult noninherited pancreatic cancer is late-onset of diabetes mellitus (DM) (age >50 years). Weight loss preceding onset of DM may also be a valuable marker to further preselect potential cancer patients among patients with new-onset DM.[40] Because the tumor itself can induce these changes in both body weight and glucose metabolism,[47] it may be possible to use similar markers to also identify patients with long-standing DM at earlier stages of pancreatic cancer. A recently published study indicated that more than half of the pancreatic cancer patients with long-standing DM exhibited weight loss of 10% or greater of their usual body weight around the time of cancer detection.[77] In another study, median fasting blood glucose levels in diabetic pancreatic cancer patients increased in the years before the cancer diagnosis, whereas median glucose levels in nonpancreatic cancer patients with long-standing DM remained fairly constant over time.[68] Finally, based on the first recorded glycated hemoglobin (HbA_{1c}) level in diabetic patients, HbA_{1c} levels of 61 mmol/mol or greater were increasingly associated with pancreatic cancer in the years prior to the cancer diagnosis, when compared with HbA_{1c} levels of 45 mmol/mol or less.[98]

As a preliminary step, we assessed the association between DM and pancreatic cancer by DM duration to evaluate whether the known association between DM and pancreatic cancer could be replicated in our study population. Our main analyses then focused only on patients with long-standing DM. In a newly matched case-control population, in which all pancreatic cancer cases and control subjects had long-standing type 2 DM, we evaluated patients in terms of glycemic control and body weight change as early markers for pancreatic cancer.

3.2.3 Methods

Study design and data source

We conducted 2 matched case-control studies using data from the United Kingdom-based Clinical Practice Research Datalink (CPRD). The CPRD is a primary care database established in 1987. It encompasses anonymized records of approximately 10 million patients who are registered with some 700 participating general practices. The general practitioners record demographics, medical diagnoses (using "Read codes"), drug prescriptions, and routine laboratory parameters, as well as additional patient characteristics such as height, weight, and smoking status.[59] Validation of diagnostic recording in the CPRD has demonstrated high accuracy and comprehensiveness of the data.[62,64] The CPRD has been used for numerous observational studies, including studies of pancreatic cancer[20,81,82] and glycemic control[85,99,100]. The present study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research (protocol no. 16_046).

First case-control study population (base population)

Pancreatic cancer case and control identification

We identified all patients 30 to 89 years of age with a first-time Read code for pancreatic cancer recorded between January 2004 and December 2013. We excluded potential cases with less than 1 year of active history in the database prior to the pancreatic cancer diagnosis. We additionally excluded patients who had a history of any other cancer (except nonmelanoma skin cancer) at any time prior to the pancreatic cancer diagnosis date, subsequently referred to as "index date". If a patient had a nonspecific incident cancer Read code within 6 months before the pancreatic cancer diagnosis, we did not exclude the case as this code was most likely related to pancreatic cancer. We then, however, shifted the index date to the date of the first recorded nonspecific cancer code.

For each pancreatic cancer case, we selected at random 4 control subjects from the CPRD population, that is, patients without a diagnosis of pancreatic cancer, matched on age (year of birth ± 2 years), sex, calendar time (using the same index date as for cases), general practice, and number of years of history in the CPRD prior to the index date (± 2 years). Eligible control subjects met the same inclusion and exclusion criteria as the cases except that control subjects with a nonspecific incident cancer Read code within 6 months prior to the index date were excluded.

Definition of DM

In the base population, we identified all patients who had diagnosed DM or probable DM (those with DM supported by biochemistry but undiagnosed) before or at the index date. We defined patients as having diagnosed DM if they met at least 1 of the following 2 criteria: (1) presence of a Read code for DM (type 1 DM, type 2 DM, or unspecified DM; without concurrent Read codes for other specific types of DM), or (2) prescriptions for antidiabetic medication with at least 1 prescription within 180 days prior to the index date. The date of the first recorded Read code for DM, or the date of the first recorded antidiabetic prescription, whichever came first, was the date of onset of diagnosed DM. We defined patients as having probable DM if (1) their last recorded HbA_{1c} level within 180 days prior to the index date was 48 mmol/mol or greater or if (2) their last recorded blood glucose level within 180 days prior to the index date (with or without a particular fasting labeling) was 7 mmol/L or greater (or ≥ 11.1 mmol/L, when recorded on the same day as an oral glucose tolerance test was done). The date of the elevated HbA_{1c} or blood glucose level characterized the onset of probable DM. We classified probable and diagnosed DM into “new-onset” DM, if the onset was at 2 years or less prior to the index date, or as “long-standing” DM, if diagnosed more than 2 years prior to the index date.

Second case-control study population (long-standing DM population)

Pancreatic cancer case and control identification

In the long-standing DM population, we included all identified pancreatic cancer cases who both met the criteria for long-standing DM as defined above and developed DM at 30 years or older (ie, had type 2 DM).[88]

For each pancreatic cancer case in the long-standing DM population, we additionally selected at random up to 10 diabetic control subjects from the CPRD population where eligible control subjects met the same inclusion and exclusion criteria as the cases except that control subjects with a nonspecific incident cancer Read code at 6 months or less prior to the index date were excluded. We matched DM cases to control subjects with DM on age (year of birth ± 3 years), sex, timing of DM onset (categorized as >2-3, >3-4, >4-5, >5-6, >6-10, or >10 years prior to the index date), calendar time, and number of years of history in the CPRD prior to the index date (± 2 years).

Definition of HbA_{1c} and blood glucose levels as well as change in body weight

We retrieved the HbA_{1c} levels recorded prior to and at the index date for each case and control subject in the long-standing DM population. We grouped HbA_{1c} levels according to 8 distinct time intervals in which the tests were recorded: 0 to 0.5, >0.5 to 1, >1 to 2, >2 to 3, >3 to 4, >4 to 5, >5 to 6, or >6 years prior to the index date. If a case or control subject had more than 1 measurement within a given time interval, we took the HbA_{1c} level recorded closest to the index date. Then, within every time interval, we grouped HbA_{1c} levels into 4 categories delineated by quartiles of HbA_{1c} levels found among control subjects in the long-standing DM population during the time between 0 and 0.5 years prior to the index date (category 1: ≤47.5 mmol/mol, category 2: 47.6-54.1 mmol/mol, category 3: 54.2-63.9 mmol/mol, and category 4: ≥64.0 mmol/mol). We also assessed blood glucose levels using the same approach. We used all entries, irrespective of whether physicians explicitly labeled them as fasting or not. However, if records of blood glucose levels coincided with the date of an oral glucose tolerance test, we only included levels specifically labeled as fasting value in our analysis. As with the HbA_{1c} levels, we divided blood glucose levels into 4 categories (category 1: ≤6.3 mmol/L, category 2: 6.4-7.9 mmol/L, category 3: 8.0-10.4 mmol/L, and category 4: ≥10.5 mmol/L).

For cases and control subjects in the long-standing DM population, we assessed both the absolute and relative changes in body weight. We defined “absolute weight change” as the difference between baseline weight and weight at index date in kilograms. We gave “relative weight change” in percentages, which expressed the absolute weight change as a fraction of the baseline weight, multiplied by 100. We defined “baseline weight” as the last weight recorded more than 3 years prior to the index date, considering it the usual adult body weight of a patient (approximately 75% in both cases and control subjects had body weight recorded within 3-4 years before the index date). “Weight at index date” was the last weight recorded at 1 year or less prior to the index date. Based on existing literature,[77,101] we grouped both absolute weight change (weight gain, >2.0 kg; stable weight, ±2.0 kg; weight loss, 2.1-4.9, 5.0-9.9, or ≥10.0 kg) and relative weight change (weight gain, >3.0%; stable weight, ±3.0%; weight loss, 3.1%-9.9%, 10.0%-14.9%, or ≥15.0%) into 5 categories.

Because assessing body weight and performing HbA_{1c} and/or blood glucose measurements during a patient’s visit were subject to the decision of the general practitioners, there existed no universal scheme for data collection.

Statistical analysis

We assessed patient characteristics in both the base and the long-standing DM populations based on recordings closest and prior to the index date. To evaluate the association between DM and pancreatic cancer in the base population, we conducted multivariable conditional logistic regression analysis and calculated odds ratios (ORs) with 95% confidence intervals (CIs). We compared those who met DM criteria with the reference group of those who did not, stratified by DM duration (new-onset vs. long-standing).

In the long-standing DM population, we evaluated - within the defined time intervals prior to the index date - the association between HbA_{1c} as well as blood glucose levels and pancreatic cancer, applying multivariable conditional logistic regression. Category 1 (ie, HbA_{1c} levels ≤47.5 mmol/mol or blood glucose levels ≤6.3 mmol/L, respectively) was the reference group. We further assessed the association between body weight change (absolute and relative), categorized by direction and magnitude of change, and pancreatic cancer. The reference group comprised long-standing DM patients who exhibited stable weights (ie, ±2.0 kg or ±3.0%, absolute and relative, respectively) prior to the index date. We evaluated the association between pancreatic cancer and concurrent severe weight loss and high HbA_{1c} level among long-standing DM patients by comparing (a) patients who suffered weight loss of 15.0% or greater alone, (b) patients who had an HbA_{1c} level of 64.0 mmol/mol or greater (≤2 years prior to the index date) alone, and (c) patients who exhibited both characteristics with patients who had neither of the 2 characteristics.

Based on existing literature,[56,58] we included a priori the following 4 variables in the multivariable models: smoking (never, current, past, unknown; all prior to the index date), body mass index (BMI) at baseline (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m², unknown; latest >3 years prior to the index date), history of pancreatitis (yes, no; >2 years prior to the index date), and alcohol consumption (none, 1-14, ≥15 U/wk, unknown; all prior to the index date). We grouped missing values for a variable of interest or for a covariate into an additional category, which implies that all cases and control subjects were included in the respective analysis. We used SAS statistical software (version 9.4; SAS Institute, Cary, NC) to conduct statistical analyses.

3.2.4 Results

Base population

We identified 3162 pancreatic cancer cases and 12,648 matched cancer-free control subjects for the base population (Figure 3.2-1). Cases were equally distributed by sex (50.8% females)

and were predominately 60 years or older (83.8%). Compared with control subjects, cases were more likely to have had a diagnosis of pancreatitis more than 2 years prior to the index date (crude OR, 2.55 [95% CI, 1.77-3.69]) and to be current or past smokers (crude OR, 1.91 [95% CI, 1.70-2.14] and 1.28 [95% CI, 1.16-1.40], respectively, compared with nonsmokers). Cases were also more likely to have a baseline BMI of 30 kg/m² or greater compared with control subjects (crude OR, 1.24 [95% CI, 1.10-1.39], compared with a normal baseline BMI of 18.5-24.9 kg/m²). Cases and control subjects did not differ significantly with regard to their weekly alcohol intake (crude OR, 1.11 [95% CI, 0.97-1.28], comparing patients with an alcohol intake of ≥15 U/wk with nondrinkers).

A total of 1093 cases (34.6%) and 1635 control subjects (12.9%) met criteria for DM prior to or at the index date (Table 3.2-1). Long-standing DM (>2 years prior to the index date) was present in 15.2% and 10.4% of cases and control subjects, respectively. While we observed an adjusted OR (aOR) for pancreatic cancer of 10.63 (95% CI, 9.11-12.41) among patients with new-onset DM, the aOR in patients with long-standing DM was 1.99 (95% CI, 1.75-2.25), when compared to nondiabetic patients.

Long-standing DM population

The analyses of glycemic control and weight change in association with pancreatic cancer were performed in 476 cases and 4724 control subjects with long-standing type 2 DM; a 10:1 match to increase power. The majority of cases (60.1%) had DM for more than 6 years prior to the index date. Cases received insulin therapy more frequently than did control subjects. Table 3.2-2 provides further descriptive characteristics of the long-standing DM population.

HbA_{1c} and blood glucose levels

In the long-standing DM population, we observed that higher HbA_{1c} levels were more strongly associated with pancreatic cancer than lower HbA_{1c} levels, when they occurred within 6 months prior to the index date (Figure 3.2-2); aORs for pancreatic cancer were 1.23 (95% CI, 0.83-1.83), 1.77 (95% CI, 1.22-2.59), and 4.94 (95% CI, 3.52-6.94) for HbA_{1c} categories 2 (47.6-54.1 mmol/mol), 3 (54.2-63.9 mmol/mol), and 4 (≥64.0 mmol/mol), respectively, compared with HbA_{1c} category 1 (≤47.5 mmol/mol). Across preceding time intervals, we observed HbA_{1c} levels within category 2 to be minimally and nonsignificantly associated with pancreatic cancer, similar to the result in the 6 months prior to the index date. In contrast, there was an association between pancreatic cancer and HbA_{1c} categories 3

and 4, which decreased with increasing time from index date. When we compared HbA_{1c} category 4 with category 1, the time intervals for >0.5 to 1 years, >1 to 2 years, and >2 to 3 years prior to the index date yielded aORs of 4.25 (95% CI, 3.04-5.93), 2.66 (95% CI, 2.00-3.54), and 1.75 (95% CI, 1.30-2.37), respectively. There were no material associations between pancreatic cancer and HbA_{1c} during the >5 to 6 years prior to the index date in any of the HbA_{1c} categories. We did not observe any association between HbA_{1c} levels and pancreatic cancer more than 6 years prior to the index date (Supplemental Table 3.2-1 http://links.lww.com/MPA/A654, which provides aORs and counts for cases and control subjects for all categories across all time intervals).

Findings for blood glucose levels were similar to HbA_{1c} findings (Figure 3.2-3). When comparing blood glucose categories 2 (6.4-7.9 mmol/L), 3 (8.0-10.4 mmol/L), and 4 (≥10.5 mmol/L) to category 1 (≤6.3 mmol/L) within 6 months prior to the index date, we found aORs for pancreatic cancer of 1.65 (95% CI, 1.00-2.70), 1.79 (95% CI, 1.10-2.91), and 4.99 (95% CI, 3.22-7.73), respectively. More than 6 months prior to the index date, we observed somewhat lower aORs for blood glucose levels, compared with HbA_{1c} levels within the corresponding categories. Overall, we found that blood glucose levels within categories 2 to 4 were associated with pancreatic cancer at >3 to 4 years prior or closer to the index date, when compared with blood glucose levels within category 1 (Supplemental Table 3.2-2 http://links.lww.com/MPA/A655, which provides aORs and counts for cases and controls for all categories across all time intervals).

Changes in body weight

In the long-standing DM population, pancreatic cancer cases were more likely to have had weight loss prior to the index date than control subjects with the risk increasing with increasing levels of weight loss (Table 3.2-3). The aORs for pancreatic cancer were 2.06 (95% CI, 1.51-2.80), 7.45 (95% CI, 5.16-10.76), and 15.40 (95% CI, 10.65-22.26) for weight loss of 3.1% to 9.9%, 10.0% to 14.9%, and 15.0% or greater, respectively, compared to stable weight. In contrast, cases were less likely to have had weight gain prior to the index date compared to control subjects (aOR, 0.59 [95% CI, 0.39-0.90]). The results were similar for the association between absolute weight change and pancreatic cancer. Although a higher proportion of the most overweight pancreatic cancer patients (baseline BMI ≥30 kg/m²) had weight loss of 15.0% or greater and/or 10.0 kg or greater; these weight losses were observed across all BMI strata.

Severe weight loss and high HbA_{1c} level

The aOR for pancreatic cancer in long-standing DM patients with concurrent weight loss of 15.0% or greater and elevated HbA_{1c} measurement of 64.0 mmol/mol or greater (≤2 years prior to the index date) was 60.97 (95% CI, 35.87-103.65), compared with patients with neither of those characteristics. Patients with concurrent weight loss 15.0% or greater and elevated HbA_{1c} measurement of 64.0 mmol/mol or greater had a 10-fold higher risk of a pancreatic cancer diagnosis than patients with weight loss of 15.0% or greater alone.

Table 3.2-1. Odds ratios for pancreatic cancer in patients with diabetes mellitus, stratified by DM duration

	Cases (N = 3162) [n (%)]	Controls (N = 12648) [n (%)]	OR crude (95% CI)	OR adjusted* (95% CI)
DM				
No	2069 (65.4)	11013 (87.1)	1 (Reference)	1 (Reference)
Yes	1093 (34.6)	1635 (12.9)	3.75 (3.41-4.12)	3.77 (3.42-4.16)
New-onset† DM	614 (19.4)	322 (2.6)	10.61 (9.11-12.35)	10.63 (9.11-12.41)
Long-standing‡ DM	479 (15.2)	1313 (10.4)	2.02 (1.80-2.28)	1.99 (1.75-2.25)

OR odds ratio, *CI* confidence interval, *DM* diabetes mellitus
* Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption
† Defined as ≤2 years prior to the index date
‡ Defined as >2 years prior to the index date

Table 3.2-2. Characteristics of pancreatic cancer cases and matched controls with long-standing diabetes mellitus (long-standing DM population)

	Cases (N = 476),*† **n (%)**	**Control Subjets (N = 4724),*** **n (%)**	**OR Crude (95% CI)**
Sex			
Male	257 (54.0)	2544 (53.9)	NA
Female	219 (46.0)	2180 (46.2)	NA
Age at index date, y			
<40	X	X	NA
40-59	38 (8.0)	366 (7.8)	NA
60-69	133 (27.9)	1339 (28.3)	NA
70-79	201 (42.2)	2016 (42.7)	NA
≥80	104 (21.9)	1003 (21.2)	NA
Diabetes duration, y			
>2-3	67 (14.1)	661 (14.0)	NA
>3-4	47 (9.9)	457 (9.7)	NA
>4-5	38 (8.0)	376 (8.0)	NA
>5-6	38 (8.0)	371 (7.9)	NA
>6-10	129 (27.1)	1290 (27.3)	NA
>10	157 (33.0)	1569 (33.2)	NA
BMI at baseline,‡ kg/m²			
<18.5	X	13 (0.3)	NA
18.5-24.9	94 (19.8)	706 (14.9)	1 (Reference)
25.0-29.9	157 (33.0)	1772 (37.5)	0.66 (0.50-0.86)

≥30.0	179 (37.6)	1866 (39.5)	0.71 (0.54-0.93)
Unknown	45 (9.5)	367 (7.8)	1.00 (0.64-1.59)
BMI at index date,§ kg/m²			
<18.5	15 (3.2)	24 (0.5)	3.62 (1.79-7.34)
18.5-24.9	152 (31.9)	736 (15.6)	1 (Reference)
25.0-29.9	142 (29.8)	1589 (33.6)	0.42 (0.33-0.54)
≥30.0	109 (22.9)	1688 (35.7)	0.30 (0.23-0.39)
Unknown	58 (12.2)	687 (14.5)	0.40 (0.29-0.56)
Smoking status			
Never	142 (29.8)	1708 (36.2)	1 (Reference)
Current	87 (18.3)	520 (11.0)	2.10 (1.57-2.82)
Past	245 (51.5)	2466 (52.2)	1.22 (0.97-1.53)
Unknown	X	30 (0.6)	NA
Alcohol consumption, U/wk			
Nondrinker	281 (59.0)	2743 (58.1)	1 (Reference)
1-14	130 (27.3)	1365 (28.9)	0.93 (0.74-1.16)
≥15	40 (8.4)	363 (7.7)	1.08 (0.75-1.55)
Unknown	25 (5.3)	253 (5.4)	0.96 (0.62-1.48)
Comorbidities			
Previous pancreatitis (>2 y prior to the index date)	14 (2.9)	59 (1.3)	2.39 (1.32-4.31)
Hypertension	321 (67.4)	3272 (69.3)	0.93 (0.75-1.14)
Dyslipidemia	139 (29.2)	1571 (33.3)	0.83 (0.67-1.02)
Ischemic heart disease	127 (26.7)	1326 (28.1)	0.93 (0.75-1.16)
Drug prescriptions			
ACE inhibitors	331 (69.5)	3389 (71.7)	0.90 (0.73-1.12)
Angiotensin II receptor blockers	112 (23.5)	1136 (24.0)	0.98 (0.78-1.23)
Statins	386 (81.1)	4018 (85.1)	0.76 (0.59-0.97)
Acetylsalicylic acid‖	322 (67.6)	3173 (67.2)	1.03 (0.84-1.26)
Proton-pump inhibitors	298 (62.6)	2090 (44.2)	2.18 (1.79-2.66)
Antidiabetic medication			
None	46 (9.7)	951 (20.1)	1 (Reference)
Oral	243 (51.1)	2914 (61.7)	2.11 (1.51-2.95)
Metformin	220 (46.2)	2591 (54.8)	
Insulin	17 (3.6)	145 (3.1)	4.14 (2.23-7.69)
Oral and insulin combined	170 (35.7)	714 (15.1)	7.97 (5.45-11.67)
Duration of insulin use,¶ y			

≤1	78 (16.4)	66 (1.4)	31.50 (19.62-50.59)
>1-2	26 (5.5)	79 (1.7)	9.79 (5.55-17.25)
>2-3	15 (3.2)	89 (1.9)	4.42 (2.32-8.43)
>3-5	26 (5.5)	169 (3.6)	4.29 (2.48-7.43)
>5-10	25 (5.3)	301 (6.4)	2.54 (1.47-4.39)
>10	17 (3.6)	155 (3.3)	3.22 (1.70-6.12)

ACE indicates angiotensin-converting enzyme; *NA*, not applicable; *X*, cell contains fewer than 5 patients (owing to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients).
* Because of rounding, percentages may not total 100.
† Pancreatic cancer patients with long-standing DM diagnosed at 30 years or older.
‡ Defined as latest recorded BMI more than 3 years prior to the index date.
§ Defined as latest recorded BMI 1 year or less prior to the index date.
‖ used as antiplatelet agent (ie, dose ≤325 mg).
¶ The reference group comprised patients without any record of an antidiabetic prescription at any time prior to (including) the index date.

Table 3.2-3. Odds ratios for pancreatic cancer associated with body weight changes in patients with long-standing DM (long-standing DM population) preceding the index date

	Cases (N = 476),*† n (%)	**Control Subjects (N = 4724),* n (%)**	**OR Crude (95% CI)**	**OR Adjusted‡ (95% CI)**
Body weight change, kg				
Weight gain: >2.0	36 (7.6)	1143 (24.2)	0.59 (0.39-0.88)	0.59 (0.39-0.89)
Stable weight: ±2.0	72 (15.1)	1345 (28.5)	1 (Reference)	1 (Reference)
Weight loss:				
2.1-4.9	45 (9.5)	586 (12.4)	1.45 (0.98-2.13)	1.51 (1.02-2.23)
5.0-9.9	93 (19.5)	493 (10.4)	3.56 (2.57-4.93)	3.72 (2.67-5.18)
≥10.0	140 (29.4)	218 (4.6)	12.19 (8.79-16.91)	13.78 (9.79-19.40)
Unknown	90 (18.9)	939 (19.9)	1.77 (1.26-2.49)	1.56 (1.05-2.32)
Body weight change, %				
Weight gain: >3.0	35 (7.4)	1090 (23.1)	0.61 (0.40-0.91)	0.59 (0.39-0.90)
Stable weight: ±3.0	79 (16.6)	1461 (30.9)	1 (Reference)	1 (Reference)
Weight loss:				
3.1-9.9	100 (21.0)	926 (19.6)	2.04 (1.50-2.77)	2.06 (1.51-2.80)
10.0-14.9	70 (14.7)	183 (3.9)	7.31 (5.09-10.50)	7.45 (5.16-10.76)
≥15.0	102 (21.4)	125 (2.7)	15.97 (11.12-22.92)	15.40 (10.65-22.26)
Unknown	90 (18.9)	939 (19.9)	1.80 (1.29-2.52)	1.54 (1.04-2.27)
Weight loss ≥15.0% and/or HbA_{1c} measurement of ≥64.0 mmol/mol (≤2 y prior to the index date)				
None	120 (25.2)	2526 (53.5)	1 (Reference)	1 (Reference)
Weight loss ≥15.0% alone	31 (6.5)	98 (2.1)	6.81 (4.32-10.73)	6.39 (4.02-10.15)
HbA_{1c} level ≥64.0 mmol/mol (category 4) alone	164 (34.5)	1109 (23.5)	3.35 (2.60-4.32)	3.40 (2.63-4.39)
Combined	70 (14.7)	24 (0.5)	64.32 (37.99-108.89)	60.97 (35.87-103.65)
Unknown§	91 (19.1)	967 (20.5)	1.98 (1.46-2.68)	1.65 (1.15-2.37)

OR odds ratio, *CI* confidence interval, *HbA_{1c}* glycated hemoglobin

* Because of rounding, percentages may not total 100.

† Pancreatic cancer patients with long-standing DM diagnosed at 30 years or older.

‡ Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption.

§ Including patients with missing information on relative change in body weight and/or HbA_{1c} measurements within 2 years prior to the index date.

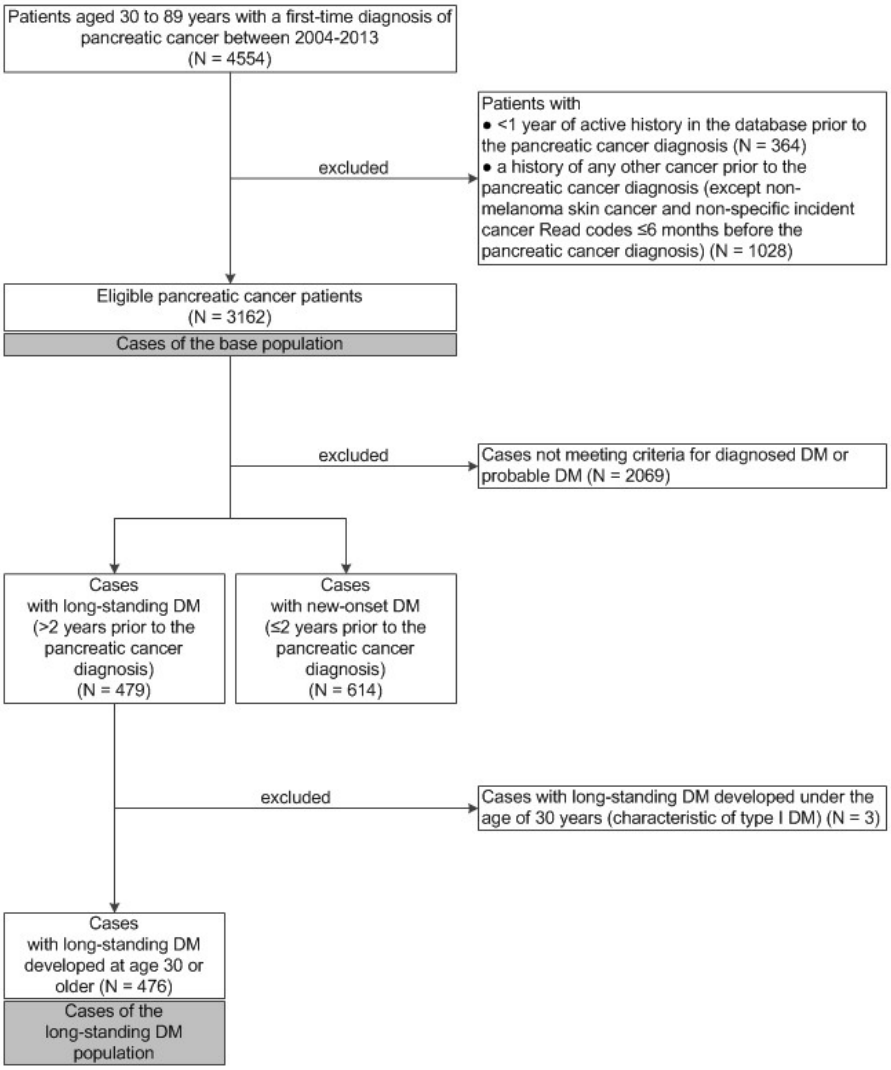
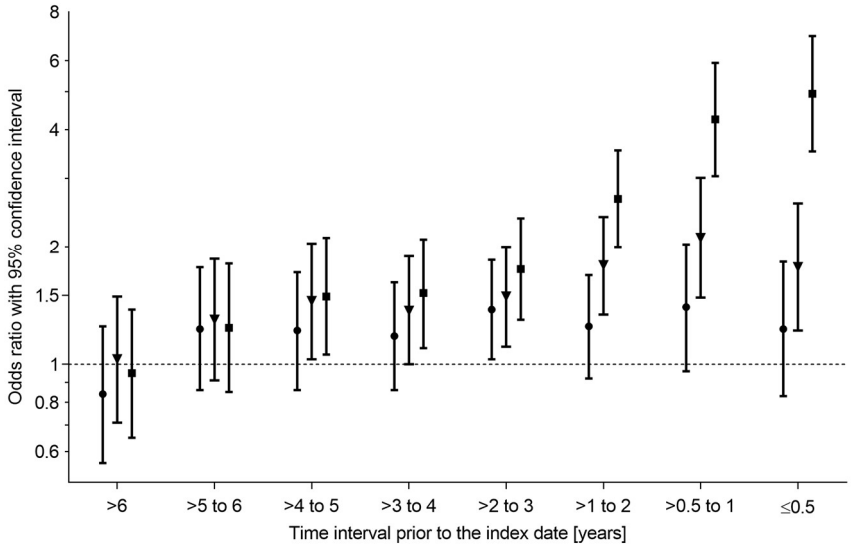
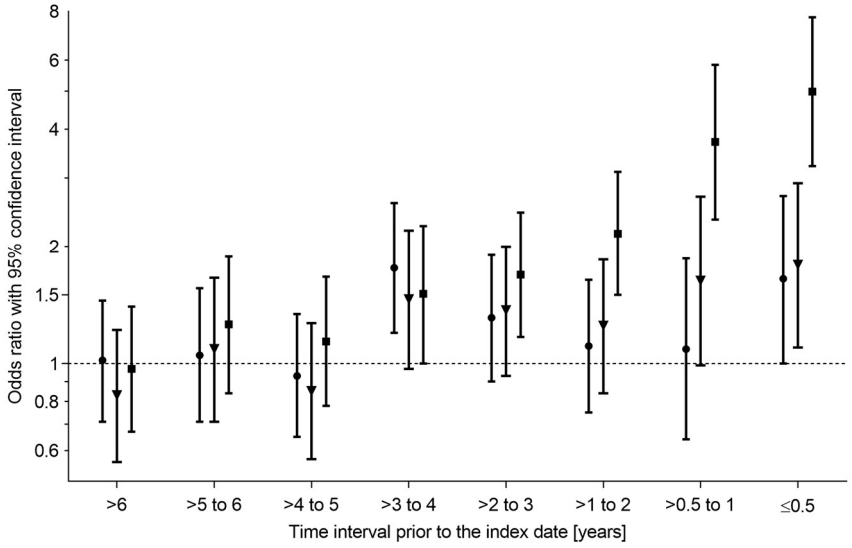


Figure 3.2-1. Approach for identifying eligible cases for the base and long-standing DM population.



Adjusted* ORs for pancreatic cancer in patients with HbA_{1c} levels of 47.6 to 54.1 mmol/mol (●), 54.2 to 63.9 mmol/mol (▼), 64.0 mmol/mol or greater (■), compared with patients with HbA_{1c} levels of 47.5 mmol/mol or less. *Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption.

Figure 3.2-2. Temporal association between different HbA_{1c} categories and pancreatic cancer in patients with long-standing DM (long-standing DM population).



Adjusted* ORs for pancreatic cancer in patients with blood glucose levels of 6.4 to 7.9 mmol/L (●), 8.0 to 10.4 mmol/L (▼), 10.5 mmol/L or greater (■), compared with patients with blood glucose levels of 6.3 mmol/L or less. *Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption.

Figure 3.2-3. Temporal association between different blood glucose categories and pancreatic cancer in patients with long-standing DM (long-standing DM population).

3.2.5 Discussion

The main objective of our study was to characterize the role of glycemic control and body weight change as early markers for pancreatic cancer in patients with long-standing type 2 DM.

Findings in the preliminary analysis within the base population (including patients with and without DM) replicated the known association between DM and pancreatic cancer.[57,102] Compared with new-onset DM, the association between long-standing DM and pancreatic cancer was not as strong. The calculated aOR for pancreatic cancer in patients with long-standing DM (1.99 [95% CI, 1.75-2.25]) was consistent with previously published findings.[50,103]

In our main analyses in the long-standing DM population, we observed that up to 4 to 5 years prior to the cancer diagnosis, poor glycemic control, especially when accompanied by HbA_{1c} levels of 64.0 mmol/mol or greater or blood glucose levels of 10.5 mmol/L or greater (highest categories), was more strongly associated with pancreatic cancer than good glycemic control (≤47.5 mmol/mol and ≤6.3 mmol/L). Of note, pancreatic cancer patients with long-standing DM were more than 2 times more likely to exhibit HbA_{1c} or blood glucose levels of the highest category compared to noncancer patients with long-standing DM within 2 years before the cancer diagnosis, and within 6 months prior to the cancer diagnosis, almost 5 times more

likely. These findings corroborate and complement results from other observational studies. One study analyzed the first recorded HbA_{1c} level of diabetic patients and found ORs for pancreatic cancer of 1.77 (95% CI, 0.99-3.19) and 0.69 (95% CI, 0.32-1.48), comparing the highest with the lowest quartile at >2 to 5 years and more than 5 years prior to the cancer diagnosis, respectively.[98] A study in patients with predominantly long-standing DM reported that the mean HbA_{1c} level was higher in pancreatic cancer patients than in noncancer patients 1 year before the cancer diagnosis.[69] Another analysis in patients with long-standing DM found somewhat higher median fasting blood glucose levels as early as 2 to 3 years prior to the cancer detection.[68]

It is noteworthy in our study that the association between HbA_{1c} levels (or blood glucose levels) within the highest category and pancreatic cancer was stronger as the proximity to the index date grew closer. Similarly, the aforementioned study showed that median fasting blood glucose levels increased continuously in pancreatic cancer patients with long-standing DM in the 5 years before the cancer diagnosis.[68] These observations indicate that pancreatic cancer patients with long-standing DM undergo similar alterations in glucose metabolism prior to the cancer diagnosis as do pancreatic cancer patients with new-onset DM. Emerging evidence suggests that new-onset DM represents a paraneoplastic feature of pancreatic cancer.[104]

Similar features in pancreatic cancer patients with long-standing DM may be responsible for the current findings. In any case, it is essential to incorporate our findings for absolute HbA_{1c} and blood glucose levels with future data focusing on the absolute or relative change in glycemic control in patients with long-standing DM. Authors of a previously published study already proposed the use of DM exacerbation as a marker to identify patients at high risk of occult pancreatic cancer among patients with early-onset DM (<55 years).[69] However, existing studies have only assessed changes in the mean (median) HbA_{1c} or blood glucose level[68,69] and have shown, as did our findings, that the sudden need for insulin therapy in patients with long-standing DM could be indicative of pancreatic cancer.[69,105] Finally, our analysis on glycemic control indicated that HbA_{1c} and blood glucose levels were similarly associated with pancreatic cancer. Some ORs for blood glucose levels were slightly lower than those for corresponding HbA_{1c} categories. This may have been caused by the erroneous recording of nonfasting rather than fasting blood glucose levels in some pancreatic cancer and noncancer patients, which would dilute the OR.

Literature suggests that apart from altering glucose metabolism, pancreatic tumors induce weight loss, preceding other symptoms of pancreatic cancer.[47,66] Thus, weight loss represents another potential criterion to identify high-risk patients for pancreatic cancer among patients with long-standing DM. In fact, we found that the association between weight loss and pancreatic cancer became stronger with increasing absolute and relative weight loss in patients with long-standing DM. More than 20% of pancreatic cancer patients, as compared with fewer than 5% of noncancer patients, had severe weight loss (≥15.0%) prior to the index date, emphasizing the potential of weight loss as a marker. One previous study in 128 pancreatic cancer patients with long-standing DM reported that prior to or around the time of cancer diagnosis, 21.1% and 41.4% of the patients lost approximately 6 to 11 kg and more than 11 kg of their body weight, respectively.[78] Another study found that some 16%, 26%, and 36% of pancreatic cancer patients with long-standing DM reported weight loss of 3.1% to 9.9%, 10.0% to 14.9%, and 15.0% or greater of their usual body weight at the time of cancer detection, respectively.[77] In both studies, data on weight loss may have also been included in the analysis when recorded after pancreatic cancer diagnosis, which could explain the higher proportions of patients experiencing serious weight loss, compared with our findings. Obviously, the presented results do not provide information on the time of onset of weight loss before cancer detection. This implies that some pancreatic cancer patients included in our study most likely did not start losing weight until they became symptomatic and suffered from cachexia.[47] In addition, the magnitude of weight loss observed in our study may only be characteristic for the time shortly before the cancer diagnosis. Thus, it will be important in the future to identify the temporal pattern of weight change resulting in severe body weight loss,

and to incorporate the latter into concepts on advancing pancreatic cancer detection in patients with long-standing DM.

Because pancreatic cancer is rare in the general population, experts have recommended a 2-sieve approach to pancreatic cancer screening where high-risk groups are identified (first sieve) and further enriched by patients with distinct pancreatic cancer markers (second sieve) before conducting detailed screening examinations.[40] Using this approach, we assessed, among patients with long-standing DM, the risk of pancreatic cancer in patients with weight loss of 15.0% or greater and concurrent elevated HbA_{1c} of 64.0 mmol/mol or greater (≤2 years prior to the index date). The result was a strong elevated risk of pancreatic cancer (aOR, 60.97 [95% CI, 35.87-103.65]), when compared with patients with neither characteristic. Notably, patients with both characteristics showed an almost 10-fold higher OR for pancreatic cancer than patients with weight loss of 15.0% or greater alone. By applying the 2 routinely and easily measured clinical variables (change in body weight and glycemic control) as markers for pancreatic cancer in an initial combined approach, we identified approximately 15% of pancreatic cancer patients with long-standing DM. At the same time, we found that only 0.5% of noncancer patients with long-standing DM had both characteristics. We suggest that these figures support the proposition to focus in more detail on the temporal pattern of body weight change, as well as on its temporal relationship with deteriorating glucose metabolism, to provide information on how exactly to apply weight loss and poor glycemic control as markers for high risk of pancreatic cancer among long-standing DM patients.

So far, research has more strongly focused on implementing pancreatic cancer screening in patients with new-onset DM rather than in patients with long-standing DM. This is because new-onset DM is probably a manifestation of pancreatic cancer, associated with a 6- to 8-fold increased risk of a diagnosis of pancreatic cancer within 3 years after its onset (age >50 years).[40] In contrast, type 2 DM represents a risk factor for pancreatic cancer, increasing the risk approximately 2-fold.[106] However, this comparison misses the point that in the long-standing type 2 DM population, patients with poor glycemic control show a 2.5- to 5-fold higher risk of having pancreatic cancer than patients with good glycemic control within 2 years before cancer detection, according to our results. Thus, it appears important to also discuss how to detect patients at high risk for pancreatic cancer among the long-standing DM population, that is, those who will benefit from further steps in pancreatic cancer screening (with poor/worsening glycemic control as an integral part of the discussion). In fact, the high global prevalence of DM (7.9%-9%)[107] challenges such ideas. A risk prediction model including different markers for pancreatic cancer may have the potential to characterize a certain proportion of long-standing DM patients who are at highest risk of pancreatic cancer, among which a relevant number of cancer patients can be identified by further screening examination.

Although this observational case-control study is based on data from a large and well-validated database, it has certain limitations. First, we analyzed all pancreatic cancers, as we were not able to distinguish between pancreatic ductal adenocarcinomas and other types of pancreatic tumors. However, ductal adenocarcinomas account for about 80% of all pancreatic cancers.[92] Thus, the impact of other types of pancreatic tumors on our findings is likely to be trivial. Second, we did not assess results with regard to pancreatic cancer stage at the time of diagnosis, given that the latter information was not available in the database. Third, although DM secondary to pancreatic cancer occurs mainly within 2 years before the cancer diagnosis,[75] it can develop within 3 to 5 years before cancer detection.[106] Therefore, we may have misclassified cancer patients with pancreatic cancer-associated DM as patients with long-standing type 2 DM. However, it is unlikely that the current findings in the long-standing DM population are primarily driven by this specific subgroup. Almost 70% of the cases in the long-standing DM population had DM for more than 5 years. Fourth, our study does not provide data on the temporal course of weight loss before pancreatic cancer detection. We have discussed in detail the implication of this point on our findings above. Fifth, noncancer patients had more missing data on HbA_{1c} and blood glucose levels within 2 years prior to the index date compared with pancreatic cancer patients. Given that we used HbA_{1c} and blood glucose levels recorded within 6 months prior to the index date to define new-onset DM, we may have overestimated the OR for pancreatic cancer associated with new-onset DM because of unavailable data for the noncancer patients. However, healthy patients are less likely to consult with their doctors, so the proportion of potentially missed new-onset DM patients among noncancer patients is probably small.

In summary, our findings indicate that the identification of patients with long-standing type 2 DM at risk for occult pancreatic cancer might be improved by using weight loss and poor glycemic control as markers. In particular, the combination of weight loss and high HbA_{1c} levels was a strong marker for pancreatic cancer. Prospective studies assessing the exact course of weight loss and worsening glycemic control may help define the predictive value of such markers in more detail.

3.2.6 Supplemental materials

Supplemental Table 3.2-1. Odds ratios for pancreatic cancer associated with different HbA_{1c} categories in patients with long-standing diabetes mellitus (long-standing DM population) within different time intervals prior to the index date

	Time interval prior to the index date							
	>6 years	>5 to 6 years	>4 to 5 years	>3 to 4 years	>2 to 3 years	>1 to 2 years	>0.5 to 1 years	≤0.5 years
HbA_{1c} category*								
1								
Cases/Controls, n	72/662	68/754	76/921	90/1088	96/1279	94/1360	55/945	50/868
aOR† (95% CI)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2								
Cases/Controls, n	43/478	61/552	68/684	80/826	104/1027	88/1083	67/856	58/855
aOR† (95% CI)	0.84 (0.56-1.25)	1.23 (0.86-1.77)	1.22 (0.86-1.72)	1.18 (0.86-1.62)	1.38 (1.03-1.85)	1.25 (0.92-1.69)	1.40 (0.96-2.03)	1.23 (0.83-1.83)
3								
Cases/Controls, n	57/521	68/591	79/686	87/801	105/970	116/990	87/771	73/793
aOR† (95% CI)	1.03 (0.71-1.49)	1.30 (0.91-1.86)	1.45 (1.03-2.04)	1.37 (1.00-1.89)	1.49 (1.11-2.00)	1.79 (1.34-2.39)	2.11 (1.48-3.01)	1.77 (1.22-2.59)
4								
Cases/Controls, n	61/600	62/564	79/652	90/747	107/848	147/864	166/758	192/788
aOR† (95% CI)	0.95 (0.65-1.38)	1.24 (0.85-1.81)	1.49 (1.06-2.11)	1.52 (1.10-2.09)	1.75 (1.30-2.37)	2.66 (2.00-3.54)	4.25 (3.04-5.93)	4.94 (3.52-6.94)
Missing values								
Cases/Controls, n	243/2463	217/2263	174/1781	129/1262	64/600	31/427	101/1394	103/1420
aOR† (95% CI)	0.77 (0.52-1.14)	0.83 (0.56-1.22)	1.02 (0.70-1.49)	1.19 (0.83-1.71)	1.37 (0.96-1.95)	1.05 (0.68-1.61)	1.27 (0.90-1.79)	1.28 (0.90-1.83)

aOR adjusted odds ratio, *CI* confidence interval, *HbA_{1c}* glycated hemoglobin

* Category 1: ≤47.5 mmol/mol, category 2: 47.6-54.1 mmol/mol, category 3: 54.2-63.9 mmol/mol, and category 4: ≥64.0 mmol/mol

† Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption

Supplemental Table 3.2-2. Odds ratios for pancreatic cancer associated with different blood glucose categories in patients with long-standing diabetes mellitus (long-standing DM population) within different time intervals prior to the index date

	Time interval prior to the index date							
	>6 years	>5 to 6 years	>4 to 5 years	>3 to 4 years	>2 to 3 years	>1 to 2 years	>0.5 to 1 years	≤0.5 years
Blood glucose category*								
1								
Cases/Controls [n]	78/757	55/575	66/584	45/629	52/634	53/662	29/433	29/427
aOR† (95% CI)	1	1	1	1	1	1	1	1
2								
Cases/Controls [n]	63/632	55/559	66/639	79/659	75/742	59/658	30/418	42/404
aOR† (95% CI)	1.02 (0.71-1.45)	1.05 (0.71-1.56)	0.93 (0.65-1.34)	1.76 (1.20-2.59)	1.31 (0.90-1.90)	1.11 (0.75-1.64)	1.09 (0.64-1.86)	1.65 (1.00-2.70)
3								
Cases/Controls [n]	50/590	44/445	47/499	57/566	68/648	58/586	41/383	46/401
aOR† (95% CI)	0.83 (0.56-1.22)	1.09 (0.71-1.66)	0.85 (0.57-1.27)	1.46 (0.97-2.20)	1.37 (0.93-2.00)	1.25 (0.84-1.85)	1.63 (0.99-2.69)	1.79 (1.10-2.91)
4								
Cases/Controls [n]	62/637	56/463	64/501	62/600	85/647	90/542	84/357	121/395
aOR† (95% CI)	0.97 (0.67-1.40)	1.26 (0.84-1.88)	1.14 (0.78-1.67)	1.51 (1.00-2.26)	1.69 (1.17-2.45)	2.16 (1.50-3.11)	3.71 (2.35-5.84)	4.99 (3.22-7.73)
Missing values								
Cases/Controls [n]	223/2108	266/2682	233/2501	233/2270	196/2053	216/2276	292/3133	238/3097
aOR† (95% CI)	1.08 (0.79-1.48)	1.00 (0.73-1.38)	0.78 (0.58-1.06)	1.45 (1.03-2.03)	1.18 (0.85-1.64)	1.19 (0.87-1.64)	1.43 (0.96-2.14)	1.16 (0.78-1.74)

aOR adjusted odds ratio, *CI* confidence interval

* Category 1: ≤6.3 mmol/L, category 2: 6.4-7.9 mmol/L, category 3: 8.0-10.4 mmol/L, and category 4: ≥10.5 mmol/L

† Adjusted for smoking status, body mass index at baseline, previous pancreatitis, and alcohol consumption

3.3 Characterization of the deterioration of diabetes control in patients with a subsequent diagnosis of pancreatic cancer

A descriptive study

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3.3.1 Abstract

Background/Objectives: Deterioration of diabetes control can be the first harbinger of pancreatic cancer. However, little is known about how to distinguish patients with pancreatic cancer-related diabetes deterioration from those with type 2 diabetes progression. We aimed to characterize the glycated hemoglobin (HbA_{1c}) and body weight profile of pancreatic cancer patients with deteriorating diabetes before the cancer diagnosis.

Methods: Using data from the UK-based Clinical Practice Research Datalink (CPRD) GOLD, we established a study population including pancreatic cancer patients with diabetes deterioration in the >0.5-3 years before the cancer diagnosis and non-cancer patients with deterioration of type 2 diabetes (comparison group). Patients were considered to have diabetes deterioration if their glucose-lowering treatment was intensified. We characterized the longitudinal trajectories of HbA_{1c} and body weight in pancreatic cancer patients compared with non-cancer patients before and after treatment intensification.

Results: The mean absolute increase in HbA_{1c} from the pre-deterioration period, i.e. the time >1-2 years before treatment intensification, to the time of treatment intensification, was 1.5% ± 1.6% in pancreatic cancer patients vs. 0.9% ± 1.4% in non-cancer patients. After treatment intensification, mean HbA_{1c} remained elevated in pancreatic cancer patients, while it returned to the pre-deterioration level in non-cancer patients. Body weight dropped by 1.9% ± 6.4% in cancer patients and increased by 0.3% ± 5.2% in non-cancer patients between the pre-deterioration period and treatment intensification, on average.

Conclusions: Pancreatic cancer-related diabetes deterioration may frequently be characterized by pronounced increases in HbA_{1c}, persistent elevation of HbA_{1c} after treatment intensification, and concomitant weight loss.

3.3.2 Introduction

Pancreatic cancer is one of the most lethal types of cancer.[12] Around 70% of all patients with pancreatic cancer die within the first year after diagnosis.[108] Early detection of the disease, at a time when pancreatic tumors still qualify for surgical resection, is considered key for an improved prognosis.[38,109]

A harbinger of pancreatic cancer is deterioration of diabetes control.[68,69,86,110] Importantly, disturbance of glucose metabolism has repeatedly been found to occur up to 2-3 years before the pancreatic cancer diagnosis[19,68,86] and thus at a time when tumors might still be resectable.[111] Of all pancreatic cancer patients, 6% to 15% have pre-existing type 2 diabetes.[50,53,86,102] In light of the high burden of type 2 diabetes[112] and the progressive nature of the disease,[113] screening all patients with deteriorating diabetes for the rare occurrence of pancreatic cancer is not justified. Rather, the focus of further medical examination should be on selected subgroups of diabetic patients with worsening glycemic control.[74] However, defining these high-risk groups requires detailed knowledge of pancreatic cancer-related diabetes deterioration.

To date, little is known about the characteristics of pancreatic cancer-related loss of diabetes control. Data on the longitudinal changes in glycated hemoglobin (HbA_{1c}) around the time of diabetes deterioration are lacking, and data on other concomitant metabolic changes are sparse. One prior study, which assessed the temporal course of HbA_{1c} and body mass index (BMI) in diabetic pancreatic cancer patients before the cancer diagnosis, reported on a continuous decrease in mean BMI accompanying the continuous increase in mean HbA_{1c} up to cancer detection.[69] More specific data on body weight changes in the subgroup of pancreatic cancer patients with diabetes deterioration are needed.

This study was conducted to compare the HbA_{1c} and body weight profiles of pancreatic cancer patients with diabetes deterioration in the >0.5 to 3 years before the cancer diagnosis with the corresponding profiles of non-cancer patients with deterioration in type 2 diabetes.

3.3.3 Methods

Study design and data source

We conducted a descriptive study using data from the United Kingdom-based Clinical Practice Research Datalink (CPRD) GOLD. CPRD GOLD is a large primary care database that holds anonymized longitudinal electronic health records on more than 15 million patients.[60,114] Data captured in the CPRD GOLD are collected by general practitioners as part of routine care. CPRD GOLD contains detailed information on demographics, medical diagnoses (using 'Read

codes'), drug prescriptions, smoking and alcohol status, laboratory test results, as well as height and body weight.[59] The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research (protocol no. 19_206) and has been made available to the journal editors.

Study population

Base population

Type 2 diabetic pancreatic cancer patients and non-cancer patients

We identified all patients in CPRD GOLD aged 51 to 90 years who had a first Read code for pancreatic cancer between January 2004 and December 2017 as well as a Read code for diabetes (type 2 diabetes or unspecified diabetes) recorded >3.5 years before the pancreatic cancer diagnosis. Of these, we excluded all patients with 1) a recorded Read code for any other cancer (except non-melanoma skin cancer) before the pancreatic cancer diagnosis, 2) a first diagnosis of diabetes before the age of 30 years (i.e. type 1 diabetes), 3) a Read code for gestational diabetes or steroid-induced diabetes at any time before the pancreatic cancer diagnosis, or 4) less than 2 HbA_{1c} measurements recorded in the >0.5 to 3 years before the diagnosis of pancreatic cancer. The date of the first diagnosis of pancreatic cancer is subsequently referred to as the index date.

For the comparison group of type 2 diabetic non-cancer patients, we identified all patients in CPRD GOLD who had a Read code for diabetes (type 2 diabetes or unspecified diabetes) and no diagnosis of pancreatic cancer in their medical records. We matched pancreatic cancer patients to non-cancer patients on the index date (i.e. used the same index date for non-cancer patients as for pancreatic cancer patients). We applied the same in- and exclusion criteria to diabetic non-cancer patients as to diabetic pancreatic cancer patients.

Assessment of deterioration of diabetes control

For each pancreatic cancer patient and non-cancer patient, we assessed presence of deterioration of diabetes control in the >0.5 to 3 years before the index date. We considered patients to have diabetes deterioration if their baseline glucose-lowering treatment was intensified. We defined baseline glucose-lowering treatment by the different anti-diabetic drug classes prescribed between >3 and 3.5 years before the index date. We required that an initial prescription for an anti-diabetic drug class was followed by ≥ 1 repeated prescription within 6 months to be considered part of the baseline glucose-lowering treatment. We defined intensification of diabetes treatment as a prescription for an anti-diabetic drug class that was

not a baseline medication. We required that the initial prescription for a non-baseline anti-diabetic drug class was followed by ≥ 1 repeated prescription within the first 6 months. The initial prescription also had to be followed by ≥ 1 prescription for each baseline medication within the first 6 months to rule out treatment switch or reduction. The latter requirement did not apply when insulin was the newly prescribed drug class. If an initial prescription for a non-baseline anti-diabetic drug class did not qualify as intensification of glucose-lowering treatment, but was classified as treatment switch or reduction, we adapted the baseline medication accordingly to identify potential treatment intensification thereafter.

Population of patients with deterioration of diabetes control

From the study base population, we selected all pancreatic cancer patients and non-cancer patients with deterioration of diabetes control.

Assessment of HbA_{1c} levels and body weight measurements

For each patient, we retrieved all HbA_{1c} levels recorded in the 10 years before the index date. We categorized HbA_{1c} levels into 1) 6-month intervals before the index date and 2) 6-month intervals before and after treatment intensification, based on the date of recording. If a patient had ≥ 2 HbA_{1c} levels recorded within a time interval, we calculated the mean of all available HbA_{1c} measurements. For the assessment of body weight measurements, we applied the same approach as for HbA_{1c}.

Statistical analysis

We described pancreatic cancer patients and non-cancer patients with or without deterioration of diabetes control in terms of demographics, diabetes duration, baseline glucose-lowering treatment, and number of HbA_{1c} levels and body weight measurements recorded between >0.5 and 3 years before the index date. Further, we described cancer and non-cancer patients with deterioration of diabetes control in terms of timing and type of treatment intensification and their pre-deterioration HbA_{1c} and BMI (both defined as mean of the measurements recorded in the >1 to 2 years before treatment intensification). To visualize the longitudinal trajectories of HbA_{1c} in pancreatic cancer and non-cancer patients with deteriorating diabetes control, we plotted mean HbA_{1c} at 6-month intervals before the index date and before and after treatment intensification for each patient group. We further plotted mean absolute change in HbA_{1c} between treatment intensification and each of the 6-month intervals before and after intensification for pancreatic cancer patients and non-cancer patients. The HbA_{1c} at treatment

intensification was the patient's (mean) HbA_{1c} in the 6 months before the date of intensification. We compared the plotted HbA_{1c} courses of pancreatic cancer patients with those of non-cancer patients and specified time windows with different HbA_{1c} trends in the two patient groups. We calculated HbA_{1c} changes in the specified time windows for pancreatic cancer and non-cancer patients. We stratified the analysis by timing of diabetes treatment intensification (>0.5-1, >1-2, or >2-3 years before the index date). For the assessment of body weight around the time of deterioration of diabetes control, we used the same approach as for the assessment of HbA_{1c}.

Stratified analyses and sensitivity analysis

We performed stratified analyses to rule out the possibility that differences in the HbA_{1c} and body weight profiles of pancreatic cancer and non-cancer patients were related to differences in the demographic and clinical characteristics of patient groups. We stratified our analysis by sex, age (≤/>70 years), diabetes duration (>3.5-5, >5-10, or >10 years before the index date), baseline glucose-lowering treatment (diet, monotherapy, dual therapy or other multiple oral drug combination, or insulin-based therapy), pre-deterioration HbA_{1c} (≤7.0%, 7.1%-8.0%, or ≥8.1%), and where applicable, by pre-deterioration BMI (<25, 25-29, or ≥30 kg/m²). We also stratified our analysis by index date (≤/>2009).

If prescriptions for an anti-diabetic drug class were dated ≥ 180 days apart at baseline, we did not capture the drug class as a baseline medication and might thus have subsequently misclassified prescription refills of the drug class as diabetes treatment intensification. Also, intensifications of diabetes treatment that were recorded closely to some prior intensification event may have been re-adjustments of the initial intervention, i.e. were follow-up intensifications, and, thus, were accompanied by metabolic changes not typically observed with deterioration of diabetes control. To assess the robustness of our primary findings, we repeated our analyses restricted to patients with a) no prior use of the anti-diabetic drug class prescribed for diabetes treatment intensification at any time in their medical history and b) no first-time prescription for any other anti-diabetic medication in the year before intensification. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3.3.4 Results

The base study population included a total of 540 pancreatic cancer patients with pre-existing type 2 diabetes and 219,627 non-cancer patients with type 2 diabetes. Among them, we identified 237 (44%) cancer patients and 76,864 (35%) non-cancer patients with deterioration of diabetes control in the >0.5 to 3 years before the index date.

Table 3.3-1 displays the demographic and clinical characteristics of pancreatic cancer patients and non-cancer patients with or without deterioration of diabetes control. In both groups, pancreatic cancer patients were older than non-cancer patients (deterioration group: 72.3 ± 8.7 vs. 67.2 ± 10.2 years), and more likely to have had diabetes for more than 5 years before the index date (83% vs. 69%) and to take anti-diabetic medication at baseline (72% vs. 48%). Additional characteristics of patients with diabetes deterioration including timing and type of treatment intensification are described in Table 3.3-2.

Population of patients with deterioration of diabetes control

HbA_{1c} profile

Figure 3.3-1 displays the trajectories of mean HbA_{1c} in pancreatic cancer and non-cancer patients before the index date, and before and after intensification of diabetes treatment (trajectories of mean HbA_{1c} stratified by timing of diabetes treatment intensification, patient characteristics, and index date are shown in Supplemental Figure 3.3-1 and Supplemental Figure 3.3-2). In the time before treatment intensification, mean HbA_{1c} rose sharply in pancreatic cancer patients and non-cancer patients, but the increase in HbA_{1c} was more pronounced in the former. Immediately after intensification of diabetes treatment, mean HbA_{1c} declined in both patient groups, but only returned to the pre-deterioration level in non-cancer patients. In pancreatic cancer patients, mean HbA_{1c} remained elevated and even started rising again in the time leading up to the index date.

Absolute increase in HbA_{1c} before the intensification of diabetes treatment

From the pre-deterioration period, i.e. the time >1 to 2 years before treatment intensification, to the time of treatment intensification, HbA_{1c} increased, on average, by 1.5% ± 1.6% in pancreatic cancer patients vs. 0.9% ± 1.4% in non-cancer patients (Table 3.3-3). Categorization of the calculated absolute HbA_{1c} changes into intervals of 0.5% revealed that increases in HbA_{1c} of ≥ 2.0% were more frequent in pancreatic cancer patients than in non-cancer patients, with 30% vs. 16% having such pronounced changes, respectively (Table 3.3-3). After stratification by timing of treatment intensification, we observed that pancreatic cancer patients had less pronounced increases in HbA_{1c} the greater the time from treatment intensification to the index date. On average, HbA_{1c} increased by 2.0% ± 1.9%, 1.6% ± 1.8%, and 1.1% ± 1.2% in pancreatic cancer patients with treatment intensification in the >0.5 to 1, >1 to 2, and >2 to 3 years before the index date, respectively. No temporal trend in HbA_{1c} increase was observed in non-cancer patients (Table 3.3-3). When we stratified our analysis

by patient characteristics, HbA_{1c} increases remained more pronounced in pancreatic cancer patients than in non-cancer patients (Supplemental Table 3.3-1). Study results did not materially change after restriction to patients with no prior use of the anti-diabetic drug class prescribed for treatment intensification and no first-time prescription for any other anti-diabetic medication in the year before intensification (Supplemental Table 3.3-2). Findings on change in HbA_{1c} between >0.5 to 1 years before treatment intensification and date of treatment intensification are shown in Table 3.3-3, Supplemental Table 3.3-2 and Supplemental Table 3.3-3.

Absolute difference in HbA_{1c} between the pre-deterioration and post-intensification period

The mean absolute difference in HbA_{1c} between the pre-deterioration period and post-intensification period, i.e. the 6-month interval after treatment intensification, was 0.9% ± 1.8% in pancreatic cancer patients compared with 0.1% ± 1.5% in non-cancer patients (Table 3.3-3). Differences in HbA_{1c} of 1.0% to 1.9% between the pre-deterioration and post-intensification period were almost twice as frequent in pancreatic cancer patients as in non-cancer patients (23% vs. 13%), and HbA_{1c} differences of ≥ 2.0% were three times more frequent (26% vs. 8%) (Table 3.3-3). In pancreatic cancer patients, HbA_{1c} differences depended on the timing of treatment intensification before the index date. In cancer patients with treatment intensification in the >0.5 to 1 years before the index date, the mean absolute difference in HbA_{1c} between the pre-deterioration and post-intensification period was 1.5% ± 2.3%, which decreased to 1.2% ± 1.6% and 0.4% ± 1.6% in cancer patients with treatment intensification in the >1 to 2 and >2 to 3 years before the index date, respectively. In non-cancer patients, HbA_{1c} differences between the pre-deterioration and post-intensification period did not differ by timing of treatment intensification (Table 3.3-3). Differences in HbA_{1c} remained more pronounced in pancreatic cancer patients than in non-cancer patients when we stratified our analysis by patient characteristics. However, this finding did not apply to patients with a pre-deterioration HbA_{1c} of ≥ 8.1%. In the latter subgroup, the mean absolute difference in HbA_{1c} was -0.3% ± 1.9% in pancreatic cancer patients and -0.8% ± 1.7% in non-cancer patients (Supplemental Table 3.3-4). Results from the sensitivity analysis were consistent with the findings from the primary analysis (Supplemental Table 3.3-2).

Body weight profile

Figure 3.3-2 displays the time courses of mean body weight in pancreatic cancer patients and non-cancer patients before the index date, and before and after diabetes treatment intensification (the time courses of mean body weight after stratification are shown in

Supplemental Figure 3.3-3 and Supplemental Figure 3.3-4 in 3.3.6 Supplemental materials). In pancreatic cancer patients, mean body weight declined continuously in the time before the intensification of diabetes treatment as well as thereafter, until cancer detection. In contrast, mean body weight remained virtually unchanged before and after diabetes treatment intensification in non-cancer patients.

Percentage change in body weight before the intensification of diabetes treatment

From the pre-deterioration period to the time of intensification of diabetes treatment, body weight decreased, on average, by 1.9% ± 6.4% in pancreatic cancer patients, whereas in non-cancer patients, body weight increased, on average, by 0.3% ± 5.2% (Table 3.3-4). Categorization of the calculated body weight changes into intervals of 0.5% revealed that weight loss of > 3% in the assessed time window was more frequent in pancreatic cancer patients than in non-cancer patients, with 37% vs. 21% having weight loss of such an amount, respectively (Table 3.3-4). Stratification by timing of treatment intensification revealed that pancreatic cancer patients had less pronounced decreases in body weight the longer treatment intensification preceded the cancer diagnosis. On average, body weight decreased by 3.6% ± 7.2%, 2.3% ± 6.6%, and 0.9% ± 5.9% in cancer patients with diabetes treatment intensification in the >0.5 to 1, >1 to 2 and >2 to 3 years before the index date, respectively. In non-cancer patients, body weight change did not depend on the timing of treatment intensification before the index date (Table 3.3-4). When we stratified our analysis by patient characteristics, we observed weight loss to remain more common in pancreatic cancer patients than in non-cancer patients. However, this finding did not apply to patients who were on diet or had an insulin-based regimen at baseline. In the aforementioned subgroups, body weight, on average, increased in pancreatic cancer and non-cancer patients before treatment intensification (diet group: 1.2% ± 5.1% vs. 0.5% ± 5.5%; insulin group: 1.4% ± 4.1% vs. 1.6% ± 6.0%) (Supplemental Table 3.3-5). Results from the sensitivity analysis were comparable with those from the primary analysis (Supplemental Table 3.3-6). Supplemental Table 3.3-7 displays the results on change in body weight between >2 to 5 years before treatment intensification and the time of intensification.

Table 3.3-1. Demographic and clinical characteristics of pancreatic cancer patients and non-cancer patients with or without deterioration of diabetes control in the >0.5 to 3 years before the index date

	No diabetes deterioration		**Diabetes deterioration**	
	Pancreatic cancer patients	**Non-cancer patients**	**Pancreatic cancer patients**	**Non-cancer patients**
	N = 303	**N = 142,763**	**N = 237**	**N = 76,864**
	[n (%)]	**[n (%)]**	**[n (%)]**	**[n (%)]**
Age at index date [years]				
51-60	21 (6.9)	30,292 (21.2)	23 (9.7)	23,182 (30.2)
61-70	84 (27.7)	41,351 (29.0)	76 (32.1)	24,835 (32.3)
71-80	121 (39.9)	44,286 (31.0)	94 (39.7)	19,574 (25.5)
81-90	77 (25.4)	26,834 (18.8)	44 (18.6)	9,273 (12.1)
Mean ± SD	73.8 ± 8.4	70.1 ± 10.5	72.3 ± 8.7	67.2 ± 10.2
Median (IQR)	74 (68-81)	70 (62-78)	72 (66-79)	67 (59-75)
Sex				
Female	131 (43.2)	63,981 (44.8)	115 (48.5)	32,117 (41.8)
Male	172 (56.8)	78,782 (55.2)	122 (51.5)	44,747 (58.2)
Index date				
2004-2006	45 (14.9)	22,913 (16.1)	46 (19.4)	13,604 (17.7)
2007-2009	61 (20.1)	28,994 (20.3)	48 (20.3)	15,193 (19.8)
2010-2012	71 (23.4)	36,018 (25.2)	64 (27.0)	19,054 (24.8)
2013-2015	88 (29.0)	37,852 (26.5)	52 (21.9)	19,680 (25.6)
2016-2017	38 (12.5)	16,986 (11.9)	27 (11.4)	9,333 (12.1)
Diabetes duration [years]				
>3.5-5	36 (11.9)	47,589 (33.3)	41 (17.3)	23,806 (31.0)
>5-10	110 (36.3)	50,298 (35.2)	109 (46.0)	28,528 (37.1)
>10	157 (51.8)	44,876 (31.4)	87 (36.7)	24,530 (31.9)
Baseline glucose-lowering treatment[a]				
Diet	47 (15.5)	40,569 (28.4)	67 (28.3)	39,836 (51.8)
Monotherapy	92 (30.4)	48,960 (34.3)	82 (34.6)	21,626 (28.1)
Metformin	70 (23.1)	38,844 (27.2)	55 (23.2)	14,702 (19.1)
Sulfonylurea	22 (7.3)	9,381 (6.6)	23 (9.7)	6,357 (8.3)
Dual therapy	69 (22.8)	27,486 (19.3)	63 (26.6)	10,819 (14.1)
Metformin + Sulfonylurea	48 (15.8)	19,012 (13.3)	43 (18.1)	7,343 (9.6)
Metformin + TZD	9 (3.0)	4,802 (3.4)	9 (3.8)	1,338 (1.7)
Triple therapy	20 (6.6)	6,159 (4.3)	12 (5.1)	1,918 (2.5)
Metformin + Sulfonylurea + TZD	14 (4.6)	3,739 (2.6)	X	875 (1.1)
Metformin + Sulfonylurea + DPP-4 inhibitor	X	1,246 (0.9)	5 (2.1)	433 (0.6)
Insulin only	29 (9.6)	8,214 (5.8)	6 (2.5)	1,617 (2.1)
Combination with insulin	42 (13.9)	11,101 (7.8)	7 (3.0)	920 (1.2)
Other	X	274 (0.2)	0	128 (0.2)

Number of HbA_{1c} recordings between >0.5 and 3 years before the index date				
Mean ± SD	4.8 ± 2.0	4.1 ± 1.7	5.6 ± 2.1	4.6 ± 2.1
Median (IQR)	5 (3-6)	4 (3-5)	6 (4-7)	4 (3-6)
Number of body weight recordings between >0.5 and 3 years before the index date				
Mean ± SD	4.4 ± 2.6	4.0 ± 2.7	5.0 ± 2.9	4.2 ± 2.8
Median (IQR)	4 (3-5)	3 (2-5)	5 (3-6)	4 (2-5)
Missing	12 (4.0)	5,280 (3.7)	6 (2.5)	2,932 (3.8)

SD standard deviation; *IQR* interquartile range; *TZD* thiazolidinedione; *DDP-4* dipeptidyl peptidase-4; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality); *HbA_{1c}* glycated hemoglobin

[a] Assessed between >3 and 3.5 years before the index date and adapted in case of treatment switch or reduction before the intensification of diabetes treatment.

Table 3.3-2. Characteristics of pancreatic cancer patients and non-cancer patients with deterioration of diabetes control in the >0.5 to 3 years before the index date

	Pancreatic cancer patients	**Non-cancer patients**
	N = 237	**N = 76,864**
	[n (%)]	**[n (%)]**
Timing of diabetes treatment intensification before the index date [years]		
>0.5-1	40 (16.9)	11,391 (14.8)
>1-1.5	46 (19.4)	14,552 (18.9)
>1.5-2	44 (18.6)	15,601 (20.3)
>2-2.5	42 (17.7)	16,466 (21.4)
>2.5-3	65 (27.4)	18,854 (24.5)
Mean ± SD	1.8 ± 0.8	1.9 ± 0.7
Median (IQR)	1.9 (1.1-2.5)	1.9 (1.3-2.5)
Type of diabetes treatment intensification		
Diet to		
Monotherapy	59 (24.9)	28,597 (37.2)
Dual therapy	6 (2.5)	5,539 (7.2)
Other therapy	X	5,700 (7.4)
Monotherapy to		
Dual therapy	75 (31.6)	20,315 (26.4)
Other therapy	7 (3.0)	1,311 (1.7)
Dual therapy to		
Triple therapy	36 (15.2)	7,507 (9.8)
Quadruple therapy	0	11 (0.0)
Insulin	7 (3.0)	711 (0.9)
Combination with insulin	20 (8.4)	2,590 (3.4)
Triple therapy to		
Quadruple therapy	X	483 (0.6)
Insulin	0	128 (0.2)
Combination with insulin	11 (4.6)	1,307 (1.7)
Other intensification	13 (5.5)	2,665 (3.5)
Pre-deterioration HbA_{1c}[a] [%]		
≤ 7.0	70 (29.5)	16,581 (21.6)
7.1-8.0	70 (29.5)	16,529 (21.5)
8.1-9.0	40 (16.9)	8,025 (10.4)
9.1-10.0	11 (4.6)	4,120 (5.4)
≥ 10.1	12 (5.1)	4,300 (5.6)
Missing	34 (14.3)	27,309 (35.5)
Mean ± SD	7.7 ± 1.3	7.8 ± 1.4

Median (IQR)	7.3 (6.8-8.3)	7.5 (6.9-8.4)
Pre-deterioration body mass index[b] [kg/m²]		
≤ 24.9	33 (13.9)	5,543 (7.2)
25.0-29.9	87 (36.7)	15,940 (20.7)
≥ 30.0	78 (32.9)	27,272 (35.5)
Missing	39 (16.5)	28,109 (36.6)
Mean ± SD	29.9 ± 6.0	31.7 ± 6.2
Median (IQR)	28.6 (26.2-32.8)	30.8 (27.4-35.1)

SD standard deviation; *IQR* interquartile range; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality); *HbA$_{1c}$* glycated hemoglobin

[a] Defined as mean of all HbA$_{1c}$ levels recorded in the >1 to 2 years before the intensification of diabetes treatment.

[b] Defined as mean of all body mass index measurements recorded in the >1 to 2 years before the intensification of diabetes treatment.

Table 3.3-3. HbA_{1c} changes in pancreatic cancer patients and non-cancer patients with deterioration of diabetes control

	Pancreatic cancer patients				**Non-cancer patients**			
	Timing of diabetes treatment intensification before the index date [years]			**Overall**	**Timing of diabetes treatment intensification before the index date [years]**			**Overall**
	>2 to 3	**>1 to 2**	**>0.5 to 1**		**>2 to 3**	**>1 to 2**	**>0.5 to 1**	
Absolute change in HbA_{1c} from >0.5 to 1 years before diabetes treatment intensification to the time of treatment intensification[a,b,c] [%]								
	N = 61	N = 57	N = 26	N = 144	N = 17,288	N = 12,935	N = 5,519	N = 35,742
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 0.9	42 (68.9)	29 (50.9)	10 (38.5)	81 (56.3)	12,250 (70.9)	9,082 (70.2)	3,882 (70.3)	25,214 (70.5)
1.0-1.4	8 (13.1)	8 (14.0)	X	19 (13.2)	2,085 (12.1)	1,671 (12.9)	684 (12.4)	4,440 (12.4)
≥ 1.5	11 (18.0)	20 (35.1)	13 (50.0)	44 (30.6)	2,953 (17.1)	2,182 (16.9)	953 (17.3)	6,088 (17.0)
In all patients with diabetes deterioration								
Mean ± SD	0.4 ± 1.5	1.4 ± 1.7	1.6 ± 1.7	1.0 ± 1.7	0.6 ± 1.3	0.7 ± 1.2	0.7 ± 1.2	0.6 ± 1.2
Median (IQR)	0.5 (-0.3;1.2)	0.9 (0.2;1.9)	1.3 (0.6;2.8)	0.8 (0.0;1.6)	0.5 (-0.0;1.1)	0.5 (0.1;1.1)	0.5 (0.1;1.1)	0.5 (0.0;1.1)
In patients with an increase in HbA_{1c} of ≥ 1.5%								
Mean ± SD	2.5 ± 1.0	3.2 ± 1.5	2.9 ± 1.1	3.0 ± 1.3	2.6 ± 1.1	2.5 ± 1.1	2.6 ± 1.2	2.6 ± 1.1
Median (IQR)	1.9 (1.6;3.6)	3.1 (1.8;4.2)	2.8 (1.8;3.5)	3.0 (1.7;3.8)	2.2 (1.8;3.0)	2.2 (1.8;3.0)	2.2 (1.8;3.0)	2.2 (1.8;3.0)
Absolute change in HbA_{1c} from the pre-deterioration period to the time of treatment intensification[a,b,c,d] [%]								
	N = 79	N = 73	N = 31	N = 183	N = 20,538	N = 17,295	N = 7,447	N = 45,280
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 0.9	38 (48.1)	32 (43.8)	11 (35.5)	81 (44.3)	12,785 (62.3)	10,033 (58.0)	4,184 (56.2)	27,002 (59.6)
1.0-1.9	25 (31.7)	19 (26.0)	X	47 (25.7)	4,595 (22.4)	4,336 (25.1)	1,951 (26.2)	10,882 (24.0)
≥ 2.0	16 (20.3)	22 (30.1)	17 (54.8)	55 (30.1)	3,158 (15.4)	2,926 (16.9)	1,312 (17.6)	7,396 (16.3)
In all patients with diabetes deterioration								
Mean ± SD	1.1 ± 1.2	1.6 ± 1.8	2.0 ± 1.9	1.5 ± 1.6	0.8 ± 1.5	1.0 ± 1.4	1.1 ± 1.3	0.9 ± 1.4
Median (IQR)	1.1 (0.5;1.8)	1.2 (0.4;2.8)	2.1 (0.5;3.0)	1.2 (0.5;2.3)	0.7 (0.0;1.4)	0.8 (0.2;1.6)	0.8 (0.3;1.6)	0.7 (0.2;1.5)
In patients with an increase in HbA_{1c} of ≥ 2.0%								

Mean ± SD	2.8 ± 0.6	3.9 ± 1.4	3.4 ± 1.1	3.4 ± 1.2	3.2 ± 1.2	3.2 ± 1.2	3.2 ± 1.2	3.2 ± 1.2
Median (IQR)	2.6 (2.3;3.4)	3.5 (2.8;4.7)	3.0 (2.4;4.3)	3.0 (2.5;4.1)	2.9 (2.3;3.8)	2.8 (2.3;3.7)	2.8 (2.3;3.8)	2.8 (2.3;3.7)
Absolute change in HbA_{1c} between the pre-deterioration period and post-intensification period[a,b,d,e] [%]								
	N = 70	N = 63	N = 35	N = 168	N = 17,340	N = 14,298	N = 6,092	N = 37,730
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 0.9	50 (71.4)	24 (38.1)	13 (37.1)	87 (51.8)	13,945 (80.4)	11,220 (78.5)	4,728 (77.6)	29,893 (79.2)
1.0-1.9	11 (15.7)	22 (34.9)	5 (14.3)	38 (22.6)	2,046 (11.8)	1,937 (13.6)	845 (13.9)	4,828 (12.8)
≥ 2.0	9 (12.9)	17 (27.0)	17 (48.6)	43 (25.6)	1,349 (7.8)	1,141 (8.0)	519 (8.5)	3,009 (8.0)
In all patients with diabetes deterioration								
Mean ± SD	0.4 ± 1.6	1.2 ± 1.6	1.5 ± 2.3	0.9 ± 1.8	-0.0 ± 1.6	0.2 ± 1.4	0.2 ± 1.4	0.1 ± 1.5
Median (IQR)	0.4 (-0.5;1.2)	1.1 (0.2;2.1)	1.9 (0.1;3.0)	0.9 (-0.1;2.0)	0.0 (-0.8;0.7)	0.1 (-0.6;0.8)	0.2 (-0.5;0.9)	0.1 (-0.6;0.8)
In patients with an increase in HbA_{1c} of ≥ 2.0%								
Mean ± SD	3.1 ± 1.3	3.1 ± 1.1	3.3 ± 1.0	3.2 ± 1.1	3.2 ± 1.1	3.1 ± 1.1	3.1 ± 1.0	3.1 ± 1.1
Median (IQR)	2.4 (2.2;4.5)	2.9 (2.4;3.4)	3.0 (2.5;3.8)	2.9 (2.4;3.8)	2.8 (2.3;3.6)	2.8 (2.3;3.5)	2.8 (2.3;3.5)	2.8 (2.3;3.6)

HbA_{1c} glycated hemoglobin; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality); *SD* standard deviation; *IQR* interquartile range

[a] The analysis included all patients with at least 1 HbA_{1c} recording for each of the 2 time windows. If patients had more than 1 HbA_{1c} level recorded within a time window, we calculated the mean of all available HbA_{1c} levels.

[b] For the definition of categorical cut-offs, we grouped HbA_{1c} increases and decreases into categories of 0.5% among pancreatic cancer and non-cancer patients. We merged adjacent categories in case they had a similar frequency ratio of pancreatic cancer patients to non-cancer patients, and kept them separate otherwise.

[c] The HbA_{1c} at treatment intensification was the patient's (mean) HbA_{1c} in the 6 months before the date of diabetes treatment intensification.

[d] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

[e] Post-intensification period was defined as the 6 months after diabetes treatment intensification.

Table 3.3-4. Body weight change in pancreatic cancer patients and non-cancer patients with deterioration of diabetes control

	Pancreatic cancer patients				Non-cancer patients			
	Timing of diabetes treatment intensification before the index date [years]			Overall	Timing of diabetes treatment intensification before the index date [years]			Overall
	>2 to 3	>1 to 2	>0.5 to 1		>2 to 3	>1 to 2	>0.5 to 1	
Relative change in body weight from the pre-deterioration period to the time of treatment intensification[a,b,c,d] [%]								
	N = 77	N = 70	N = 30	N = 177	N = 18,479	N = 14,413	N = 5,978	N = 38,870
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
None or gain	31 (40.3)	25 (35.7)	8 (26.7)	64 (36.2)	9,800 (53.0)	7,698 (53.4)	3,121 (52.2)	20,619 (53.1)
Loss:								
0.1-3.0	23 (29.9)	18 (25.7)	7 (23.3)	48 (27.1)	4,737 (25.6)	3,873 (26.9)	1,625 (27.2)	10,235 (26.3)
≥ 3.1	23 (29.9)	27 (38.6)	15 (50.0)	65 (36.7)	3,942 (21.3)	2,842 (19.7)	1,232 (20.6)	8,016 (20.6)
In all patients with diabetes deterioration								
Mean ± SD	-0.9 ± 5.9	-2.3 ± 6.6	-3.6 ± 7.2	-1.9 ± 6.4	0.2 ± 5.3	0.3 ± 5.1	0.1 ± 5.0	0.3 ± 5.2
Median (IQR)	-0.7 (-3.5;1.7)	-1.8 (-5.8;2.4)	-3.0 (-10.2;0.0)	-1.6 (-4.8;1.5)	0.0 (-2.5;2.8)	0.0 (-2.3;2.7)	0.0 (-2.4;2.6)	0.0 (-2.4;2.7)
In patients with weight loss of ≥ 3.1%								
Mean ± SD	-7.2 ± 4.7	-8.4 ± 5.5	-8.9 ± 4.3	-8.1 ± 4.9	-6.2 ± 3.6	-6.1 ± 3.5	-6.2 ± 3.6	-6.2 ± 3.6
Median (IQR)	-5.0 (-10.2;-3.7)	-7.5 (-9.6;-4.4)	-10.2 (-12.8;-5.1)	-6.0 (-11.7;-4.2)	-5.1 (-7.3;-3.9)	-5.0 (-7.0;-3.9)	-5.3 (-7.2;-3.8)	-5.1 (-7.2;-3.9)

SD standard deviation; *IQR* interquartile range

[a] The analysis included all patients with at least 1 body weight measurement for each of the 2 time window. If patients had more than 1 body weight measurement recorded within a time window, we calculated the mean of all available body weight recordings.

[b] For the definition of categorical cut-offs, we grouped body weight increases and decreases into categories of 0.5% among pancreatic cancer and non-cancer patients. We merged adjacent categories in case they had a similar frequency ratio of pancreatic cancer patients to non-cancer patients, and kept them separate otherwise.

[c] The body weight at treatment intensification was the patient's (mean) weight in the 6 months before the date of diabetes treatment intensification.

[d] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

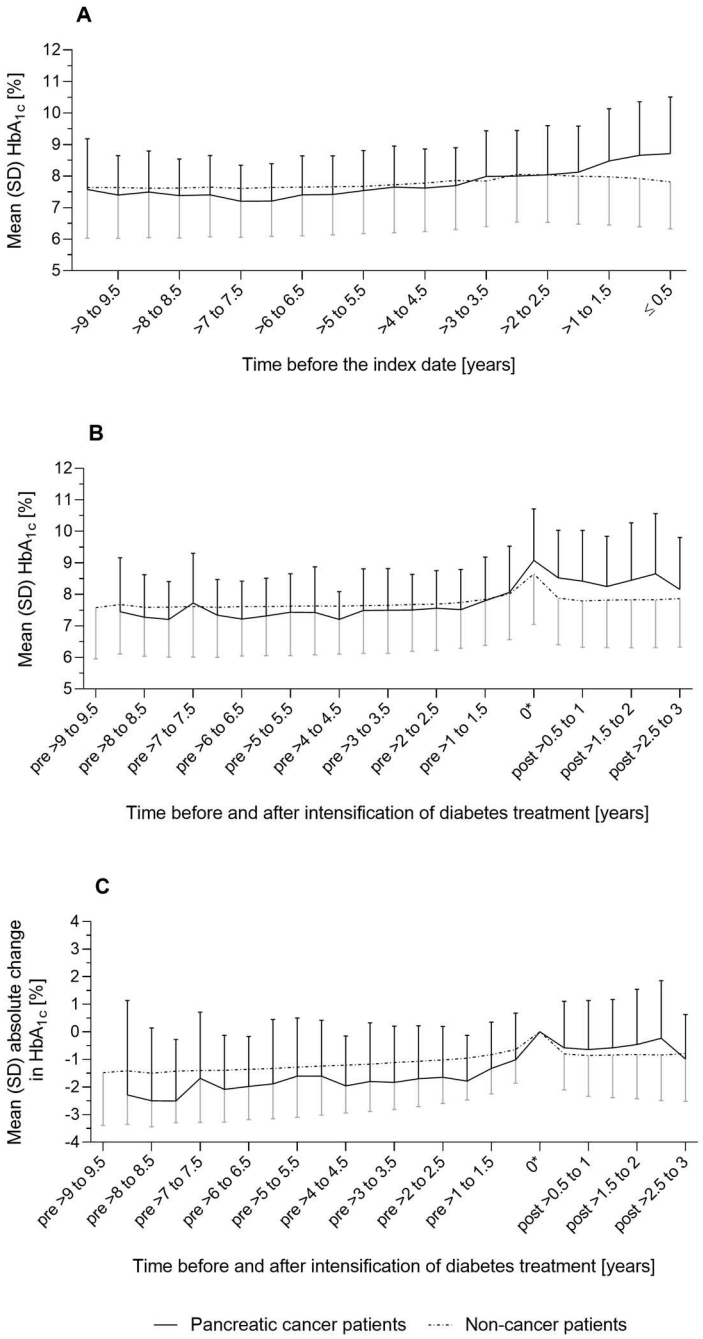


Figure 3.3-1. The temporal course of HbA_{1c} in pancreatic cancer patients and non-cancer patients with diabetes deterioration in the >0.5 to 3 years before the index date

(A) Mean HbA_{1c} in the time before the index date (B) Mean HbA_{1c} in the time before and after intensification of diabetes treatment (C) Mean absolute change in HbA_{1c} from diabetes treatment intensification at each of the 6-month intervals before and after intensification

*The HbA_{1c} at diabetes treatment intensification was the patient's (mean) HbA_{1c} in the 6 months before the date of intensification.

The minimum number of data points required to calculate mean HbA_{1c} or mean absolute HbA_{1c} change for a time interval was set to 5. *HbA_{1c}* glycated hemoglobin; *SD* standard deviation

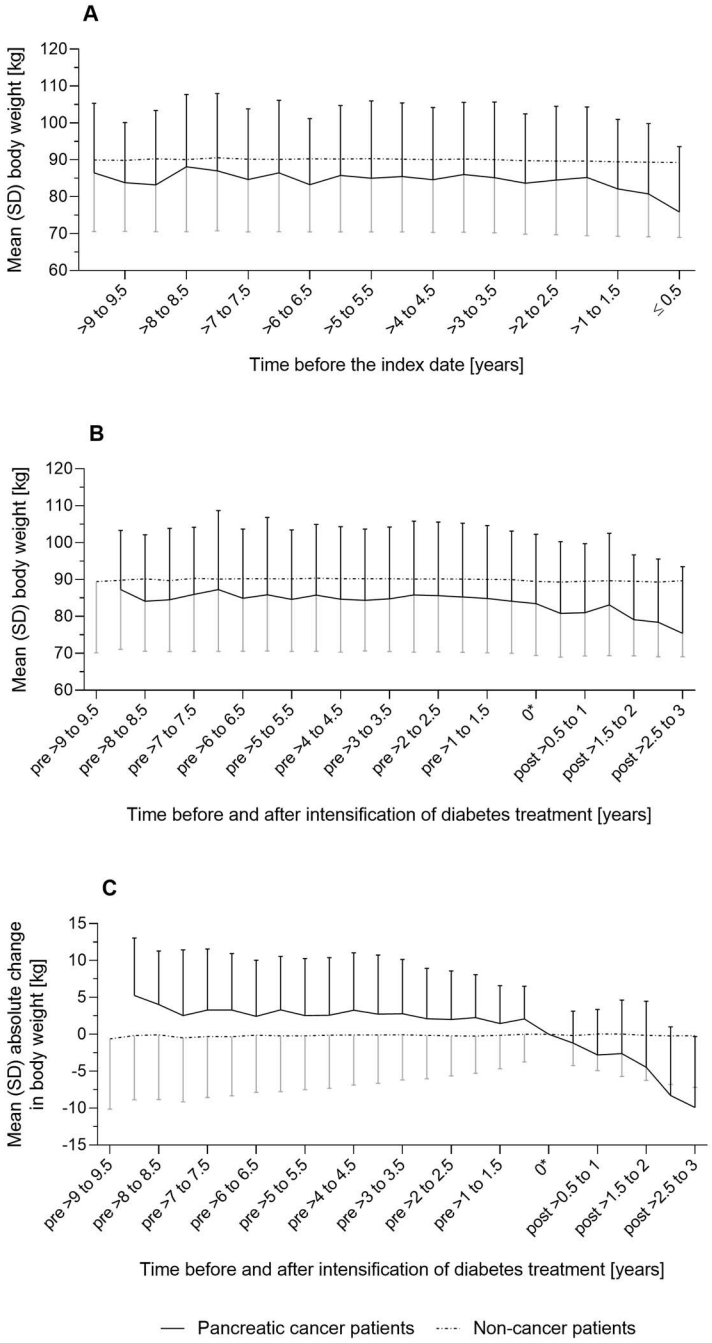


Figure 3.3-2. The temporal course of body weight in pancreatic cancer patients and non-cancer patients with diabetes deterioration in the >0.5 to 3 years before the index date

(A) Mean body weight in the time before the index date (B) Mean body weight in the time before and after intensification of diabetes treatment (C) Mean absolute change in body weight from diabetes treatment intensification at each of the 6-month intervals before and after intensification

*The body weight at diabetes treatment intensification was the patient's (mean) body weight in the 6 months before the date of intensification.

The minimum number of data points required to calculate mean body weight or mean absolute weight change for a time interval was set to 5. *SD* standard deviation

3.3.5 Discussion

This primary care database study provides important data on the HbA_{1c} and body weight profile of patients with pancreatic cancer-related deterioration of diabetes control. We observed that pancreatic cancer patients had pronounced increases in HbA_{1c} before the intensification of diabetes treatment and showed persistent elevation of HbA_{1c} after intensification. HbA_{1c} increases of ≥ 2.0% from >1 to 2 years before treatment intensification to the time of intensification, and ≥ 1.5% from >0.5 to 1 years before treatment intensification, were more frequent in pancreatic cancer patients than in non-cancer patients with type 2 diabetes progression, as were HbA_{1c} differences of ≥ 1.0% between the pre-deterioration and post-intensification period. Pancreatic cancer patients continuously lost body weight at the time of diabetes deterioration and thereafter, until cancer detection. Weight loss of > 3.0% from >1 to 2 years before treatment intensification to the time of intensification was more common in pancreatic cancer patients than in non-cancer patients.

Deterioration of diabetes control has previously been identified as a harbinger of pancreatic cancer. In two studies, median blood glucose and mean HbA_{1c} increased continuously in pancreatic cancer patients with pre-existing diabetes in the time leading up to the cancer diagnosis.[68,69] Further, our prior study in type 2 diabetes patients reported on an increasing association between HbA_{1c} levels of ≥ 8% and the risk of pancreatic cancer with closer proximity to the cancer diagnosis.[86] Finally, short-term use of insulin (<5 years) was found to be associated with an almost 5-fold elevated risk for pancreatic cancer when compared with no insulin use among diabetic patients.[69] Findings on the presence of cancer-related diabetes deterioration up to 2-3 years before the pancreatic cancer diagnosis are currently of little use for the early detection of the disease, given the lack of criteria for identifying subjects at high risk of pancreatic cancer and, thus, in need of further medical examinations among the large population of patients with deteriorating diabetes.

Our study provided evidence that steep HbA_{1c} increases at the time of diabetes deterioration and persistent HbA_{1c} elevation after diabetes treatment intensification may be characteristic features of pancreatic cancer-related diabetes deterioration. The study also suggests that deterioration of diabetes control among pancreatic cancer patients may frequently be characterized by concomitant weight loss. The latter finding complements results of an earlier study, which showed that the continuous increase in mean HbA_{1c} before the pancreatic cancer diagnosis coincided with a continuous decrease in mean BMI among diabetic patients.[69] Rapid increase in blood glucose and concomitant decrease in body weight are metabolic changes

that have repeatedly been associated with pancreatic cancer-related new onset of diabetes.[66,79,115] Our results fit well with these findings.

In this study, we observed among pancreatic cancer patients that the magnitude of HbA_{1c} increases and the amount of weight loss decreased with increasing lead-time between diabetes deterioration and subsequent cancer diagnosis. Thus, it may be that the extent of HbA_{1c} and body weight change in patients with pancreatic cancer-related diabetes deterioration depends on the timing of deterioration before the cancer diagnosis. Another explanation for the temporal trend in metabolic changes could be that the earlier diabetes deterioration occurs before the pancreatic cancer diagnosis, the less likely it is caused by the tumor, but rather represents a manifestation of type 2 diabetes progression. Either way, current findings suggest that pancreatic cancer patients have deterioration of diabetes control characterized by pronounced HbA_{1c} increases or concomitant weight loss mainly in the 1 to 2 years before the cancer diagnosis.

In the United Kingdom, 6% to 15%[50,53,86,102] of the 10,500 annually diagnosed pancreatic cancer patients[116] have pre-existing type 2 diabetes, but approximately 3.7 million British people have diagnosed type 2 diabetes.[117] The figures indicate that deterioration of typical type 2 diabetes is much more prevalent than pancreatic cancer-related deterioration of diabetes control, which means that the predictive value of HbA_{1c} and body weight changes for the presence of pancreatic cancer will be low. As such, considerations to promote pancreatic cancer work-up in subjects with diabetes deterioration/anti-diabetic treatment failure and concurrent weight loss do not seem justified given the high burden of unnecessarily performed medical examinations.[118] For now, efforts may be limited to focusing on close follow-up of patients who have diabetes deterioration with steep HbA_{1c} increases, persistent elevation of HbA_{1c} after treatment intensification and/or unexplained weight loss, and to further medical examinations, if clinical or laboratory abnormalities occur. Regular HbA_{1c} testing recommended for diabetic patients[119] may offer a good opportunity to monitor these patients.

In the current study, we defined patients as having deterioration of diabetes control when they received intensification of diabetes treatment, i.e. were prescribed an additional anti-diabetic drug class or insulin. We did not identify presence of diabetes deterioration based on increases in anti-diabetic drug dosage, because dose adjustments are difficult to evaluate in the CPRD GOLD. Furthermore, the study population did not include patients with deterioration of diabetes control that remained untreated or was addressed by lifestyle changes. Thus, our findings are limited to pancreatic cancer patients who have diabetes deterioration along with subsequent modification of diabetes treatment other than dosage change.

Some additional limitations need to be considered. First, pancreatic cancer stage was not captured in the CPRD GOLD data. Second, weight graphs suggested that body weight declines continuously beyond the time of diabetes treatment intensification in pancreatic cancer patients, but not in non-cancer patients. Due to limited data, we were not able to characterize body weight change beyond the time of intensification in more detail. Third, HbA_{1c} levels and body weight measurements were not available for all patients at each time interval. The analyses of HbA_{1c} changes at the time of diabetes deterioration included 61%-77% and 47%-59% of pancreatic cancer patients and non-cancer patients, respectively, the analysis of body weight change included 75% of pancreatic cancer patients and 51% of non-cancer patients.

In conclusion, pancreatic cancer-related deterioration of diabetes control may frequently be characterized by pronounced increases in HbA_{1c}, persistent elevation of HbA_{1c} after treatment intensification, and concomitant weight loss. The future meaning of observed changes in HbA_{1c} and body weight for the prediction of pancreatic cancer risk will depend on whether additional clinical or molecular characteristics of pancreatic cancer-related diabetes deterioration will be identified.

3.3.6 Supplemental materials

Supplemental Table 3.3-1. Absolute change in HbA_{1c} from the pre-deterioration period to the time of treatment intensification in pancreatic cancer patients and non-cancer patients, stratified by patient characteristics and index date[a]

		Absolute change in HbA_{1c} [%]				
		Categories			**Mean ± SD**	**Median (IQR)**
		≤ 0.9	**1.0-1.9**	**≥ 2.0**		
Sex						
Pancreatic cancer patients	Female (N = 89)	37 (41.6)	23 (25.8)	29 (32.6)	1.5 ± 1.4	1.2 (0.5;2.3)
	Male (N = 94)	44 (46.8)	24 (25.5)	26 (27.7)	1.5 ± 1.8	1.1 (0.4;2.3)
Non-cancer patients	Female (N = 18,457)	11,029 (59.8)	4,378 (23.7)	3,050 (16.5)	0.9 ± 1.4	0.7 (0.2;1.5)
	Male (N = 26,823)	15,973 (59.6)	6,504 (24.3)	4,346 (16.2)	0.9 ± 1.5	0.7 (0.2;1.5)
Age at index date [years]						
Pancreatic cancer patients	51-70 (N = 75)	27 (36.0)	22 (29.3)	26 (34.7)	1.6 ± 1.5	1.5 (0.5;2.6)
	≥ 71 (N = 108)	54 (50.0)	25 (23.2)	29 (26.9)	1.4 ± 1.7	1.0 (0.4;2.2)
Non-cancer patients	51-70 (N = 28,757)	16,790 (58.4)	6,966 (24.2)	5,001 (17.4)	0.9 ± 1.5	0.8 (0.1;1.6)
	≥ 71 (N = 16,523)	10,212 (61.8)	3,916 (23.7)	2,395 (14.5)	0.9 ± 1.4	0.7 (0.2;1.4)
Diabetes duration [years]						
Pancreatic cancer patients	>3.5-5 (N = 28)	11 (39.3)	9 (32.1)	8 (28.6)	1.6 ± 1.8	1.2 (0.5;2.8)
	>5-10 (N = 84)	32 (38.1)	23 (27.4)	29 (34.5)	1.6 ± 1.5	1.4 (0.6;2.4)
	> 10 (N = 71)	38 (53.5)	15 (21.1)	18 (25.4)	1.3 ± 1.7	0.8 (0.2;2.0)
Non-cancer patients	>3.5-5 (N = 16,032)	9,591 (59.8)	3,738 (23.3)	2,703 (16.9)	0.9 ± 1.6	0.7 (0.1;1.5)
	>5-10 (N = 17,391)	10,043 (57.8)	4,455 (25.6)	2,893 (16.6)	1.0 ± 1.3	0.8 (0.3;1.6)
	> 10 (N = 11,857)	7,368 (62.1)	2,689 (22.7)	1,800 (15.2)	0.8 ± 1.4	0.7 (0.0;1.4)
Baseline glucose-lowering treatment[b]						
Pancreatic cancer patients	Diet (N = 44)	21 (47.7)	15 (34.1)	8 (18.2)	1.2 ± 1.1	1.1 (0.5;1.5)
	Monotherapy (N = 62)	16 (25.8)	16 (25.8)	30 (48.4)	2.1 ± 1.6	1.8 (1.0;3.0)

	Dual therapy or other multiple oral drug combination (N = 67)	36 (53.7)	14 (20.9)	17 (25.4)	1.2 ± 1.8	0.8 (0.2;2.0)
	Insulin-based therapy (N = 10)	8 (80.0)	X	0	0.1 ± 0.7	0.1 (-0.2;0.9)
Non-cancer patients	Diet (N = 15,571)	8,846 (56.8)	4,144 (26.6)	2,581 (16.6)	1.1 ± 1.3	0.8 (0.4;1.5)
	Monotherapy (N = 17,119)	10,293 (60.1)	3,982 (23.3)	2,844 (16.6)	0.8 ± 1.5	0.7 (0.1;1.5)
	Dual therapy or other multiple oral drug combination (N = 10,695)	6,485 (60.6)	2,429 (22.7)	1,781 (16.7)	0.8 ± 1.5	0.7 (0.0;1.5)
	Insulin-based therapy (N = 1,895)	1,378 (72.7)	327 (17.3)	190 (10.0)	0.3 ± 1.5	0.3 (-0.4;1.1)
Pre-deterioration HbA_{1c}[c] [%]						
Pancreatic cancer patients	≤ 7.0 (N = 61)	19 (31.2)	23 (37.7)	19 (31.2)	1.8 ± 1.5	1.3 (0.8;2.7)
	7.1-8.0 (N = 67)	28 (41.8)	12 (17.9)	27 (40.3)	1.8 ± 1.6	1.3 (0.5;2.8)
	≥ 8.1 (N = 55)	34 (61.8)	12 (21.8)	9 (16.4)	0.7 ± 1.5	0.4 (-0.3;1.5)
Non-cancer patients	≤ 7.0 (N = 15,262)	7,059 (46.3)	4,811 (31.5)	3,392 (22.2)	1.4 ± 1.3	1.1 (0.6;1.9)
	7.1-8.0 (N = 15,353)	9,207 (60.0)	3,695 (24.1)	2,451 (16.0)	1.0 ± 1.2	0.8 (0.3;1.5)
	≥ 8.1 (N = 14,665)	10,736 (73.2)	2,376 (16.2)	1,553 (10.6)	0.2 ± 1.5	0.2 (-0.7;1.1)
Index date						
Pancreatic cancer patients	2004-2009 (N = 67)	33 (49.3)	18 (26.9)	16 (23.9)	1.3 ± 1.6	1.0 (0.3;1.9)
	≥ 2010 (N = 116)	48 (41.4)	29 (25.0)	39 (33.6)	1.6 ± 1.6	1.2 (0.5;2.5)
Non-cancer patients	2004-2009 (N = 16,737)	10,081 (60.2)	4,111 (24.6)	2,545 (15.2)	0.8 ± 1.4	0.7 (0.1;1.5)
	≥ 2010 (N = 28,543)	16,921 (59.3)	6,771 (23.7)	4,851 (17.0)	0.9 ± 1.5	0.7 (0.2;1.5)

HbA_{1c} glycated hemoglobin; *SD* standard deviation; *IQR* interquartile range; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

[a] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

[b] Assessed between >3 and 3.5 years before the index date and adapted in case of treatment switch or reduction before the intensification of diabetes treatment.

[c] Defined as mean of all HbA_{1c} levels recorded in the >1 to 2 years before the intensification of diabetes treatment.

Supplemental Table 3.3-2. Sensitivity analysis of HbA_{1c} changes in pancreatic cancer patients and non-cancer patients with no prior use of the anti-diabetic drug class prescribed for diabetes treatment intensification at any time in their medical history and no first-time prescription for any other anti-diabetic medication in the year before intensification

	Pancreatic cancer patients				**Non-cancer patients**			
	Timing of diabetes treatment intensification before the index date [years]			**Overall**	**Timing of diabetes treatment intensification before the index date [years]**			**Overall**
	>2 to 3	**>1 to 2**	**>0.5 to 1**		**>2 to 3**	**>1 to 2**	**>0.5 to 1**	
Absolute change in HbA_{1c} from >0.5 to 1 years before diabetes treatment intensification to the time of treatment intensification[a,b,c] [%]								
	N = 39	N = 47	N = 25	N = 111	N = 12,284	N = 10,881	N = 4,654	N = 27,819
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 0.9	24 (61.5)	22 (46.8)	9 (36.0)	55 (49.6)	8,535 (69.5)	7,633 (70.2)	3,299 (70.9)	19,467 (70.0)
1.0-1.4	6 (15.4)	7 (14.9)	X	16 (14.4)	1,571 (12.8)	1,436 (13.2)	580 (12.5)	3,587 (12.9)
≥ 1.5	9 (23.1)	18 (38.3)	13 (52.0)	40 (36.0)	2,178 (17.7)	1,812 (16.7)	775 (16.7)	4,765 (17.1)
In all patients with diabetes deterioration								
Mean ± SD	0.7 ± 1.5	1.5 ± 1.8	1.8 ± 1.5	1.3 ± 1.7	0.7 ± 1.2	0.7 ± 1.1	0.7 ± 1.2	0.7 ± 1.2
Median (IQR)	0.6 (0.0;1.5)	1.1 (0.4;2.1)	1.6 (0.7;2.8)	1.0 (0.3;1.8)	0.5 (0.1;1.1)	0.5 (0.1;1.1)	0.5 (0.1;1.1)	0.5 (0.1;1.1)
In patients with an increase in HbA_{1c} of ≥ 1.5%								
Mean ± SD	2.4 ± 1.0	3.3 ± 1.6	2.9 ± 1.1	3.0 ± 1.3	2.6 ± 1.1	2.5 ± 1.1	2.6 ± 1.2	2.6 ± 1.1
Median (IQR)	1.8 (1.6;3.3)	3.3 (1.7;4.3)	2.8 (1.8;3.5)	3.1 (1.7;3.8)	2.2 (1.7;3.0)	2.2 (1.7;3.0)	2.2 (1.8;3.0)	2.2 (1.7;3.0)
Absolute change in HbA_{1c} from the pre-deterioration period to the time of treatment intensification[a,b,c,d] [%]								
	N = 53	N = 62	N = 29	N = 144	N = 15,301	N = 14,618	N = 6,337	N = 36,256
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 0.9	27 (50.9)	23 (37.1)	9 (31.0)	59 (41.0)	9,430 (61.6)	8,456 (57.9)	3,558 (56.2)	21,444 (59.2)
1.0-1.9	14 (26.4)	18 (29.0)	X	35 (24.3)	3,559 (23.3)	3,727 (25.5)	1,686 (26.6)	8,972 (24.8)
≥ 2.0	12 (22.6)	21 (33.9)	17 (58.6)	50 (34.7)	2,312 (15.1)	2,435 (16.7)	1,093 (17.3)	5,840 (16.1)
In all patients with diabetes deterioration								

Mean ± SD	1.1 ± 1.2	1.8 ± 1.9	2.3 ± 1.7	1.7 ± 1.7	0.8 ± 1.5	1.0 ± 1.3	1.1 ± 1.3	0.9 ± 1.4
Median (IQR)	0.9 (0.5;1.8)	1.3 (0.6;2.9)	2.2 (0.6;3.0)	1.2 (0.5;2.8)	0.7 (0.1;1.4)	0.8 (0.3;1.6)	0.8 (0.3;1.6)	0.8 (0.2;1.5)
In patients with an increase in HbA_{1c} of ≥ 2.0%								
Mean ± SD	2.8 ± 0.7	4.0 ± 1.4	3.4 ± 1.1	3.5 ± 1.2	3.2 ± 1.2	3.2 ± 1.2	3.2 ± 1.2	3.2 ± 1.2
Median (IQR)	2.7 (2.4;3.4)	3.5 (2.9;4.7)	3.0 (2.4;4.3)	3.1 (2.6;4.3)	2.8 (2.3;3.8)	2.8 (2.3;3.7)	2.8 (2.3;3.8)	2.8 (2.3;3.7)

Absolute change in HbA_{1c} between the pre-deterioration period and post-intensification period[a,b,d,e] [%]

	N = 46 n (%)	N = 54 n (%)	N = 32 n (%)	N = 132 n (%)	N = 12,568 n (%)	N = 12,011 n (%)	N = 5,154 n (%)	N = 29,733 n (%)
≤ 0.9	31 (67.4)	19 (35.2)	11 (34.4)	61 (46.2)	10,172 (80.9)	9,504 (79.1)	4,038 (78.4)	23,714 (79.8)
1.0-1.9	7 (15.2)	20 (37.0)	5 (15.6)	32 (24.2)	1,484 (11.8)	1,601 (13.3)	696 (13.5)	3,781 (12.7)
≥ 2.0	8 (17.4)	15 (27.8)	16 (50.0)	39 (29.6)	912 (7.3)	906 (7.5)	420 (8.2)	2,238 (7.5)
In all patients with diabetes deterioration								
Mean ± SD	0.7 ± 1.6	1.2 ± 1.5	1.8 ± 1.8	1.2 ± 1.6	-0.0 ± 1.5	0.2 ± 1.4	0.2 ± 1.4	0.1 ± 1.4
Median (IQR)	0.5 (-0.0;1.5)	1.3 (0.2;2.1)	2.0 (0.3;3.0)	1.1 (0.1;2.2)	0.0 (-0.7;0.7)	0.1 (-0.5;0.8)	0.2 (-0.4;0.9)	0.1 (-0.6;0.8)
In patients with an increase in HbA_{1c} of ≥ 2.0%								
Mean ± SD	3.2 ± 1.4	2.9 ± 0.7	3.2 ± 1.0	3.1 ± 1.0	3.2 ± 1.2	3.1 ± 1.1	3.1 ± 1.1	3.1 ± 1.1
Median (IQR)	2.4 (2.2;4.7)	2.8 (2.4;3.1)	3.0 (2.5;3.8)	2.8 (2.4;3.8)	2.8 (2.3;3.6)	2.7 (2.3;3.5)	2.7 (2.3;3.5)	2.8 (2.3;3.5)

HbA_{1c} glycated hemoglobin; *SD* standard deviation; *IQR* interquartile range; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

[a] The analysis included all patients with at least 1 HbA_{1c} recording for each of the 2 time windows. If patients had more than 1 HbA_{1c} level recorded within a time window, we calculated the mean of all available HbA_{1c} levels.

[b] For the definition of categorical cut-offs, we grouped HbA_{1c} increases and decreases into categories of 0.5% among pancreatic cancer and non-cancer patients. We merged adjacent categories in case they had a similar frequency ratio of pancreatic cancer patients to non-cancer patients, and kept them separate otherwise.

[c] The HbA_{1c} at treatment intensification was the patient's (mean) HbA_{1c} in the 6 months before the date of diabetes treatment intensification.

[d] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

[e] Post-intensification period was defined as the 6 months after diabetes treatment intensification.

Supplemental Table 3.3-3. Absolute change in HbA_{1c} from >0.5 to 1 years before diabetes treatment intensification to the time of treatment intensification in pancreatic cancer patients and non-cancer patients, stratified by patient characteristics and index date

		Absolute change in HbA_{1c} [%]				
		Categories			**Mean ± SD**	**Median (IQR)**
		≤ 0.9	**1.0-1.4**	**≥ 1.5**		
Sex						
Pancreatic cancer patients	Female (N = 65)	34 (52.3)	11 (16.9)	20 (30.8)	1.2 ± 1.4	0.8 (0.3;1.7)
	Male (N = 79)	47 (59.5)	8 (10.1)	24 (30.4)	0.9 ± 1.9	0.7 (-0.1;1.6)
Non-cancer patients	Female (N = 14,734)	10,529 (71.5)	1,738 (11.8)	2,467 (16.7)	0.6 ± 1.2	0.5 (0.0;1.1)
	Male (N = 21,008)	14,685 (69.9)	2,702 (12.9)	3,621 (17.2)	0.6 ± 1.2	0.5 (0.0;1.1)
Age at index date [years]						
Pancreatic cancer patients	51-70 (N = 64)	33 (51.6)	10 (15.6)	21 (32.8)	1.1 ± 1.8	0.9 (0.1;1.7)
	≥ 71 (N = 80)	48 (60.0)	9 (11.3)	23 (28.8)	1.0 ± 1.6	0.7 (0.0;1.6)
Non-cancer patients	51-70 (N = 22,465)	15,583 (69.4)	2,879 (12.8)	4,003 (17.8)	0.6 ± 1.3	0.5 (0.0;1.2)
	≥ 71 (N = 13,277)	9,631 (72.5)	1,561 (11.8)	2,085 (15.7)	0.6 ± 1.2	0.5 (0.0;1.1)
Diabetes duration [years]						
Pancreatic cancer patients	>3.5-5 (N = 21)	10 (47.6)	X	7 (33.3)	1.0 ± 1.8	1.2 (0.0;2.6)
	>5-10 (N = 68)	35 (51.5)	11 (16.2)	22 (32.4)	1.1 ± 1.5	0.9 (0.3;1.6)
	> 10 (N = 55)	36 (65.5)	X	15 (27.3)	1.0 ± 1.9	0.5 (-0.2;1.6)
Non-cancer patients	>3.5-5 (N = 13,321)	9,186 (69.0)	1,692 (12.7)	2,443 (18.3)	0.7 ± 1.3	0.5 (0.1;1.2)
	>5-10 (N = 13,040)	9,240 (70.9)	1,642 (12.6)	2,158 (16.6)	0.7 ± 1.2	0.5 (0.1;1.1)
	> 10 (N = 9,381)	6,788 (72.4)	1,106 (11.8)	1,487 (15.9)	0.5 ± 1.2	0.4 (-0.1;1.1)
Baseline glucose-lowering treatment[a]						
Pancreatic cancer patients	Diet (N = 28)	14 (50.0)	9 (32.1)	5 (17.9)	1.1 ± 1.2	0.9 (0.3;1.4)
	Monotherapy (N = 49)	23 (46.9)	X	23 (46.9)	1.5 ± 1.8	1.2 (0.5;2.8)

	Dual therapy or other multiple oral drug combination (N = 58)	36 (62.1)	6 (10.3)	16 (27.6)	0.8 ± 1.7	0.6 (-0.2;1.6)
	Insulin-based therapy (N = 9)	8 (88.9)	X	0	-0.4 ± 1.7	-0.2 (-0.7;0.5)
Non-cancer patients	Diet (N = 11,806)	8,266 (70.0)	1,554 (13.2)	1,986 (16.8)	0.8 ± 1.2	0.6 (0.2;1.1)
	Monotherapy (N = 13,611)	9,525 (70.0)	1,703 (12.5)	2,383 (17.5)	0.6 ± 1.3	0.5 (0.0;1.1)
	Dual therapy or other multiple oral drug combination (N = 8,801)	6,245 (71.0)	1,029 (11.7)	1,527 (17.4)	0.5 ± 1.2	0.4 (-0.1;1.1)
	Insulin-based therapy (N = 1,524)	1,178 (77.3)	154 (10.1)	192 (12.6)	0.2 ± 1.2	0.2 (-0.5;0.9)
Pre-deterioration HbA_{1c}[b] [%]						
Pancreatic cancer patients	≤ 7.0 (N = 44)	20 (45.5)	8 (18.2)	16 (36.4)	1.5 ± 1.7	1.1 (0.3;2.0)
	7.1-8.0 (N = 50)	26 (52.0)	X	20 (40.0)	1.3 ± 1.7	0.9 (0.3;2.2)
	≥ 8.1 (N = 41)	29 (70.7)	7 (17.1)	5 (12.2)	0.2 ± 1.4	0.5 (-0.3;1.1)
	Missing (N = 9)	6 (66.7)	0	X	0.6 ± 1.6	0.3 (-0.4;1.6)
Non-cancer patients	≤ 7.0 (N = 10,011)	6,746 (67.4)	1,367 (13.7)	1,898 (19.0)	0.9 ± 1.2	0.6 (0.2;1.2)
	7.1-8.0 (N = 10,635)	7,661 (72.0)	1,374 (12.9)	1,600 (15.0)	0.7 ± 1.1	0.5 (0.1;1.1)
	≥ 8.1 (N = 10,282)	7,338 (71.4)	1,197 (11.6)	1,747 (17.0)	0.5 ± 1.3	0.4 (-0.3;1.1)
	Missing (N = 4,814)	3,469 (72.1)	502 (10.4)	843 (17.5)	0.4 ± 1.5	0.4 (-0.2;1.1)
Index date						
Pancreatic cancer patients	2004-2009 (N = 55)	31 (56.4)	9 (16.4)	15 (27.3)	0.9 ± 1.7	0.7 (-0.2;1.6)
	≥ 2010 (N = 89)	50 (56.2)	10 (11.2)	29 (32.6)	1.1 ± 1.7	0.8 (0.3;1.7)
Non-cancer patients	2004-2009 (N = 13,573)	9,565 (70.5)	1,706 (12.6)	2,302 (17.0)	0.6 ± 1.2	0.5 (0.0;1.1)
	≥ 2010 (N = 22,169)	15,649 (70.6)	2,734 (12.3)	3,786 (17.1)	0.7 ± 1.2	0.5 (0.0;1.1)

HbA_{1c} glycated hemoglobin; *SD* standard deviation; *IQR* interquartile range; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

[a] Assessed between >3 and 3.5 years before the index date and adapted in case of treatment switch or reduction before the intensification of diabetes treatment.

[b] Defined as mean of all HbA_{1c} levels recorded in the >1 to 2 years before the intensification of diabetes treatment.

Supplemental Table 3.3-4. Absolute change in HbA_{1c} between the pre-deterioration period and post-intensification period in pancreatic cancer patients and non-cancer patients, stratified by patient characteristics and index date[a,b]

		Absolute change in HbA_{1c} [%]				
		Categories			**Mean ± SD**	**Median (IQR)**
		≤ 0.9	**1.0-1.9**	**≥ 2.0**		
Sex						
Pancreatic cancer patients	Female (N = 78)	37 (47.4)	20 (25.6)	21 (26.9)	1.2 ± 1.8	1.1 (-0.0;2.1)
	Male (N = 90)	50 (55.6)	18 (20.0)	22 (24.4)	0.7 ± 1.8	0.7 (-0.5;1.9)
Non-cancer patients	Female (N = 15,549)	12,237 (78.7)	2,036 (13.1)	1,276 (8.2)	0.1 ± 1.5	0.1 (-0.6;0.8)
	Male (N = 22,181)	17,656 (79.6)	2,792 (12.6)	1,733 (7.8)	0.1 ± 1.5	0.1 (-0.6;0.8)
Age at index date [years]						
Pancreatic cancer patients	51-70 (N = 72)	39 (54.2)	14 (19.4)	19 (26.4)	0.8 ± 1.7	0.7 (0.0;2.1)
	≥ 71 (N = 96)	48 (50.0)	24 (25.0)	24 (25.0)	1.0 ± 1.9	1.0 (-0.3;2.0)
Non-cancer patients	51-70 (N = 23,472)	18,278 (77.9)	3,147 (13.4)	2,047 (8.7)	0.1 ± 1.6	0.1 (-0.7;0.9)
	≥ 71 (N = 14,258)	11,615 (81.5)	1,681 (11.8)	962 (6.8)	0.1 ± 1.4	0.1 (-0.5;0.7)
Diabetes duration [years]						
Pancreatic cancer patients	>3.5-5 (N = 29)	12 (41.4)	7 (24.1)	10 (34.5)	1.0 ± 1.8	1.2 (0.0;2.4)
	>5-10 (N = 76)	36 (47.4)	23 (30.3)	17 (22.4)	1.1 ± 1.8	1.1 (0.0;1.9)
	> 10 (N = 63)	39 (61.9)	8 (12.7)	16 (25.4)	0.7 ± 1.8	0.5 (-0.5;2.1)
Non-cancer patients	>3.5-5 (N = 13,057)	10,369 (79.4)	1,701 (13.0)	987 (7.6)	0.1 ± 1.6	0.1 (-0.6;0.8)
	>5-10 (N = 14,481)	11,403 (78.7)	1,871 (12.9)	1,207 (8.3)	0.2 ± 1.4	0.1 (-0.5;0.8)
	> 10 (N = 10,192)	8,121 (79.7)	1,256 (12.3)	815 (8.0)	0.0 ± 1.5	-0.0 (-0.8;0.8)
Baseline glucose-lowering treatment[c]						
Pancreatic cancer patients	Diet (N = 36)	16 (44.4)	9 (25.0)	11 (30.6)	1.3 ± 1.3	1.1 (0.4;2.4)
	Monotherapy (N = 59)	21 (35.6)	19 (32.2)	19 (32.2)	1.3 ± 1.9	1.3 (-0.1;2.4)

	Dual therapy or other multiple oral drug combination (N = 64)	42 (65.6)	10 (15.6)	12 (18.8)	0.6 ± 1.7	0.5 (-0.4;1.6)
	Insulin-based therapy (N = 9)	8 (88.9)	0	X	-1.0 ± 2.3	-0.8 (-1.1;0.3)
Non-cancer patients	Diet (N = 13,141)	10,164 (77.4)	1,911 (14.5)	1,066 (8.1)	0.4 ± 1.3	0.3 (-0.2;0.9)
	Monotherapy (N = 14,017)	11,327 (80.8)	1,618 (11.5)	1,072 (7.7)	-0.0 ± 1.5	-0.0 (-0.8;0.7)
	Dual therapy or other multiple oral drug combination (N = 8,992)	7,084 (78.8)	1,121 (12.5)	787 (8.8)	-0.1 ± 1.6	-0.1 (-1.0;0.8)
	Insulin-based therapy (N = 1,580)	1,318 (83.4)	178 (11.3)	84 (5.3)	-0.3 ± 1.6	-0.2 (-1.1;0.6)
Pre-deterioration HbA_{1c}[d] [%]						
Pancreatic cancer patients	≤ 7.0 (N = 57)	22 (38.6)	17 (29.8)	18 (31.6)	1.6 ± 1.5	1.3 (0.5;2.8)
	7.1-8.0 (N = 62)	28 (45.2)	13 (21.0)	21 (33.9)	1.3 ± 1.5	1.1 (0.1;2.1)
	≥ 8.1 (N = 49)	37 (75.5)	8 (16.3)	X	-0.3 ± 1.9	-0.4 (-1.4;0.9)
Non-cancer patients	≤ 7.0 (N = 12,679)	8,860 (69.9)	2,319 (18.3)	1,500 (11.8)	0.8 ± 1.2	0.5 (0.0;1.2)
	7.1-8.0 (N = 12,927)	10,417 (80.6)	1,567 (12.1)	943 (7.3)	0.3 ± 1.1	0.1 (-0.4;0.7)
	≥ 8.1 (N = 12,124)	10,616 (87.6)	942 (7.8)	566 (4.7)	-0.8 ± 1.7	-0.8 (-1.7;0.2)
Index date						
Pancreatic cancer patients	2004-2009 (N = 64)	34 (53.1)	14 (21.9)	16 (25.0)	0.9 ± 1.7	0.8 (-0.2;2.0)
	≥ 2010 (N = 104)	53 (51.0)	24 (23.1)	27 (26.0)	0.9 ± 1.9	0.9 (-0.1;2.1)
Non-cancer patients	2004-2009 (N = 14,400)	11,435 (79.4)	1,867 (13.0)	1,098 (7.6)	0.1 ± 1.5	0.1 (-0.7;0.8)
	≥ 2010 (N = 23,330)	18,458 (79.1)	2,961 (12.7)	1,911 (8.2)	0.1 ± 1.5	0.1 (-0.6;0.8)

HbA_{1c} glycated hemoglobin; *SD* standard deviation; *IQR* interquartile range; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

[a] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

[b] Post-intensification period was defined as the 6 months after diabetes treatment intensification.

[c] Assessed between >3 and 3.5 years before the index date and adapted in case of treatment switch or reduction before the intensification of diabetes treatment.

[d] Defined as mean of all HbA_{1c} levels recorded in the >1 to 2 years before the intensification of diabetes treatment.

Supplemental Table 3.3-5. Relative change in body weight from the pre-deterioration period to the time of treatment intensification in pancreatic cancer patients and non-cancer patients, stratified by patient characteristics and index date[a]

		Relative change in body weight [%]				
		Categories			Mean ± SD	Median (IQR)
		None or gain	Loss of ≤ 3.0	Loss of ≥ 3.1		
Sex						
Pancreatic cancer patients	Female (N = 83)	28 (33.7)	23 (27.7)	32 (38.6)	-2.7 ± 6.5	-2.2 (-5.4;1.0)
	Male (N = 94)	36 (38.3)	25 (26.6)	33 (35.1)	-1.2 ± 6.4	-1.4 (-4.4;2.5)
Non-cancer patients	Female (N = 15,735)	8,244 (52.4)	3,893 (24.7)	3,598 (22.9)	0.2 ± 5.7	0.0 (-2.7;2.9)
	Male (N = 23,135)	12,375 (53.5)	6,342 (27.4)	4,418 (19.1)	0.3 ± 4.8	0.0 (-2.3;2.6)
Age at index date [years]						
Pancreatic cancer patients	51-70 (N = 75)	27 (36.0)	17 (22.7)	31 (41.3)	-2.1 ± 6.4	-1.7 (-5.0;1.6)
	≥ 71 (N = 102)	37 (36.3)	31 (30.4)	34 (33.3)	-1.8 ± 6.5	-1.5 (-4.5;1.3)
Non-cancer patients	51-70 (N = 25,103)	13,449 (53.6)	6,632 (26.4)	5,022 (20.0)	0.3 ± 5.1	0.1 (-2.3;2.8)
	≥ 71 (N = 13,767)	7,170 (52.1)	3,603 (26.2)	2,994 (21.8)	0.1 ± 5.3	0.0 (-2.5;2.5)
Diabetes duration [years]						
Pancreatic cancer patients	>3.5-5 (N = 28)	14 (50.0)	X	10 (35.7)	-1.2 ± 7.2	-0.6 (-4.8;3.7)
	>5-10 (N = 82)	27 (32.9)	23 (28.1)	32 (39.0)	-2.5 ± 6.2	-2.1 (-5.0;1.0)
	> 10 (N = 67)	23 (34.3)	21 (31.3)	23 (34.3)	-1.5 ± 6.4	-1.3 (-4.8;2.0)
Non-cancer patients	>3.5-5 (N = 14,156)	7,914 (55.9)	3,470 (24.5)	2,772 (19.6)	0.5 ± 5.4	0.4 (-2.2;3.1)
	>5-10 (N = 14,749)	7,612 (51.6)	4,066 (27.6)	3,071 (20.8)	0.1 ± 4.9	0.0 (-2.4;2.4)
	> 10 (N = 9,965)	5,093 (51.1)	2,699 (27.1)	2,173 (21.8)	0.0 ± 5.3	0.0 (-2.6;2.6)
Baseline glucose-lowering treatment[b]						
Pancreatic cancer patients	Diet (N = 42)	27 (64.3)	8 (19.1)	7 (16.7)	1.2 ± 5.1	0.9 (-1.8;4.6)
	Monotherapy (N = 62)	14 (22.6)	13 (21.0)	35 (56.5)	-3.9 ± 6.3	-3.5 (-5.9;-0.6)

	Dual therapy or other multiple oral drug combination (N = 65)	19 (29.2)	23 (35.4)	23 (35.4)	-2.4 ± 6.8	-1.8 (-5.5;0.5)
	Insulin-based therapy (N = 8)	X	X	0	1.4 ± 4.1	0.5 (-1.6;3.1)
Non-cancer patients	Diet (N = 13,812)	7,710 (55.8)	3,461 (25.1)	2,641 (19.1)	0.5 ± 5.5	0.3 (-2.2;3.0)
	Monotherapy (N = 14,433)	7,387 (51.2)	3,914 (27.1)	3,132 (21.7)	0.0 ± 4.9	0.0 (-2.6;2.4)
	Dual therapy or other multiple oral drug combination (N = 8,995)	4,468 (49.7)	2,522 (28.0)	2,005 (22.3)	-0.1 ± 5.0	-0.1 (-2.7;2.5)
	Insulin-based therapy (N = 1,630)	1,054 (64.7)	338 (20.7)	238 (14.6)	1.6 ± 6.0	1.3 (-1.2;4.2)
Pre-deterioration HbA_{1c}[c] [%]						
Pancreatic cancer patients	≤ 7.0 (N = 61)	32 (52.5)	8 (13.1)	21 (34.4)	-0.1 ± 6.8	0.0 (-3.9;4.7)
	7.1-8.0 (N = 59)	16 (27.1)	16 (27.1)	27 (45.8)	-2.9 ± 5.4	-2.4 (-5.1;0.0)
	≥ 8.1 (N = 45)	12 (26.7)	21 (46.7)	12 (26.7)	-2.5 ± 6.6	-1.5 (-3.3;0.0)
	Missing (N = 12)	X	X	5 (41.7)	-4.1 ± 7.3	-2.2 (-9.2;1.1)
Non-cancer patients	≤ 7.0 (N = 12,043)	7,715 (64.1)	2,559 (21.3)	1,769 (14.7)	1.3 ± 5.5	1.1 (-1.3;3.8)
	7.1-8.0 (N = 12,188)	6,145 (50.4)	3,598 (29.5)	2,445 (20.1)	-0.1 ± 4.5	0.0 (-2.4;2.1)
	≥ 8.1 (N = 11,243)	5,129 (45.6)	3,181 (28.3)	2,933 (26.1)	-0.5 ± 5.1	-0.5 (-3.1;2.1)
	Missing (N = 3,396)	1,630 (48.0)	897 (26.4)	869 (25.6)	-0.1 ± 6.0	-0.3 (-3.1;2.6)
Pre-deterioration body mass index[d] [kg/m²]						
Pancreatic cancer patients	< 25 (N = 29)	13 (44.8)	6 (20.7)	10 (34.5)	-0.7 ± 7.4	-1.3 (-3.9;3.2)
	25-29 (N = 74)	25 (33.8)	23 (31.1)	26 (35.1)	-1.9 ± 6.1	-1.5 (-4.5;0.8)
	≥ 30 (N = 74)	26 (35.1)	19 (25.7)	29 (39.2)	-2.3 ± 6.4	-1.9 (-5.8;1.5)
Non-cancer patients	< 25 (N = 4,227)	2,453 (58.0)	916 (21.7)	858 (20.3)	1.1 ± 7.1	0.6 (-2.2;3.8)
	25-29 (N = 12,541)	6,946 (55.4)	3,314 (26.4)	2,281 (18.2)	0.5 ± 5.0	0.2 (-2.1;2.8)
	≥ 30 (N = 22,102)	11,220 (50.8)	6,005 (27.2)	4,877 (22.1)	-0.1 ± 4.8	0.0 (-2.6;2.5)
Index date						
Pancreatic cancer patients	2004-2009 (N = 64)	26 (40.6)	16 (25.0)	22 (34.4)	-1.8 ± 6.4	-1.5 (-5.5;2.5)

	≥ 2010 (N = 113)	38 (33.6)	32 (28.3)	43 (38.1)	-1.9 ± 6.5	-1.7 (-4.6;1.0)|
Non-cancer patients	2004-2009 (N = 14,782)	7,945 (53.8)	3,872 (26.2)	2,965 (20.1)	0.3 ± 5.2	0.0 (-2.3;2.7)
	≥ 2010 (N = 24,088)	12,674 (52.6)	6,363 (26.4)	5,051 (21.0)	0.2 ± 5.2	0.0 (-2.5;2.7)

SD standard deviation; *IQR* interquartile range; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

[a] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

[b] Assessed between >3 and 3.5 years before the index date and adapted in case of treatment switch or reduction before the intensification of diabetes treatment.

[c] Defined as mean of all HbA_{1c} levels recorded in the >1 to 2 years before the intensification of diabetes treatment.

[d] Defined as mean of all body mass index measurements recorded in the >1 to 2 years before the intensification of diabetes treatment.

Supplemental Table 3.3-6. Sensitivity analysis of body weight change in pancreatic cancer patients and non-cancer patients with no prior use of the anti-diabetic drug class prescribed for diabetes treatment intensification at any time in their medical history and no first-time prescription for any other anti-diabetic medication in the year before intensification

	Pancreatic cancer patients				**Non-cancer patients**			
	Timing of diabetes treatment intensification before the index date [years]			**Overall**	**Timing of diabetes treatment intensification before the index date [years]**			**Overall**
	>2 to 3	**>1 to 2**	**>0.5 to 1**		**>2 to 3**	**>1 to 2**	**>0.5 to 1**	
Relative change in body weight from the pre-deterioration period to the time of treatment intensification[a,b,c,d] [%]								
	N = 53	N = 60	N = 29	N = 142	N = 13,828	N = 12,250	N = 5,100	N = 31,178
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
None or gain	23 (43.4)	22 (36.7)	7 (24.1)	52 (36.6)	7,372 (53.3)	6,578 (53.7)	2,669 (52.3)	16,619 (53.3)
Loss:								
0.1-3.0	16 (30.2)	14 (23.3)	7 (24.1)	37 (26.1)	3,674 (26.6)	3,329 (27.2)	1,397 (27.4)	8,400 (26.9)
≥ 3.1	14 (26.4)	24 (40.0)	15 (51.7)	53 (37.3)	2,782 (20.1)	2,343 (19.1)	1,034 (20.3)	6,159 (19.8)
In all patients with diabetes deterioration								
Mean ± SD	-0.3 ± 5.4	-2.3 ± 6.8	-4.0 ± 6.9	-1.9 ± 6.4	0.3 ± 5.0	0.4 ± 5.0	0.1 ± 4.9	0.3 ± 5.0
Median (IQR)	-0.5 (-3.1;1.7)	-1.8 (-5.9;2.5)	-3.1 (-10.2;-0.9)	-1.7 (-4.8;1.5)	0.0 (-2.4;2.6)	0.0 (-2.2;2.7)	0.0 (-2.4;2.5)	0.0 (-2.3;2.6)
In patients with weight loss of ≥ 3.1%								
Mean ± SD	-6.1 ± 4.5	-8.4 ± 5.5	-8.9 ± 4.3	-7.9 ± 5.0	-6.0 ± 3.4	-6.0 ± 3.5	-6.2 ± 3.5	-6.0 ± 3.4
Median (IQR)	-4.6 (-5.7;-3.5)	-6.9 (-9.3;-4.5)	-10.2 (-12.8;-5.1)	-5.9 (-10.4;-4.2)	-5.0 (-6.9;-3.8)	-5.0 (-6.9;-3.8)	-5.2 (-7.2;-3.8)	-5.0 (-7.0;-3.8)

SD standard deviation; *IQR* interquartile range

[a] The analysis included all patients with at least 1 body weight measurement for each of the 2 time windows. If patients had more than 1 body weight measurement recorded within a time window, we calculated the mean of all available body weight recordings.

[b] For the definition of categorical cut-offs, we grouped body weight increases and decreases into categories of 0.5% among pancreatic cancer and non-cancer patients. We merged adjacent categories in case they had a similar frequency ratio of pancreatic cancer patients to non-cancer patients, and kept them separate otherwise.

[c] The body weight at treatment intensification was the patient's (mean) weight in the 6 months before the date of diabetes treatment intensification.

[d] Pre-deterioration period was defined as the time between >1 and 2 years before the intensification of diabetes treatment.

Supplemental Table 3.3-7. Additional calculations on body weight change in pancreatic cancer patients and non-cancer patients with deterioration of diabetes control

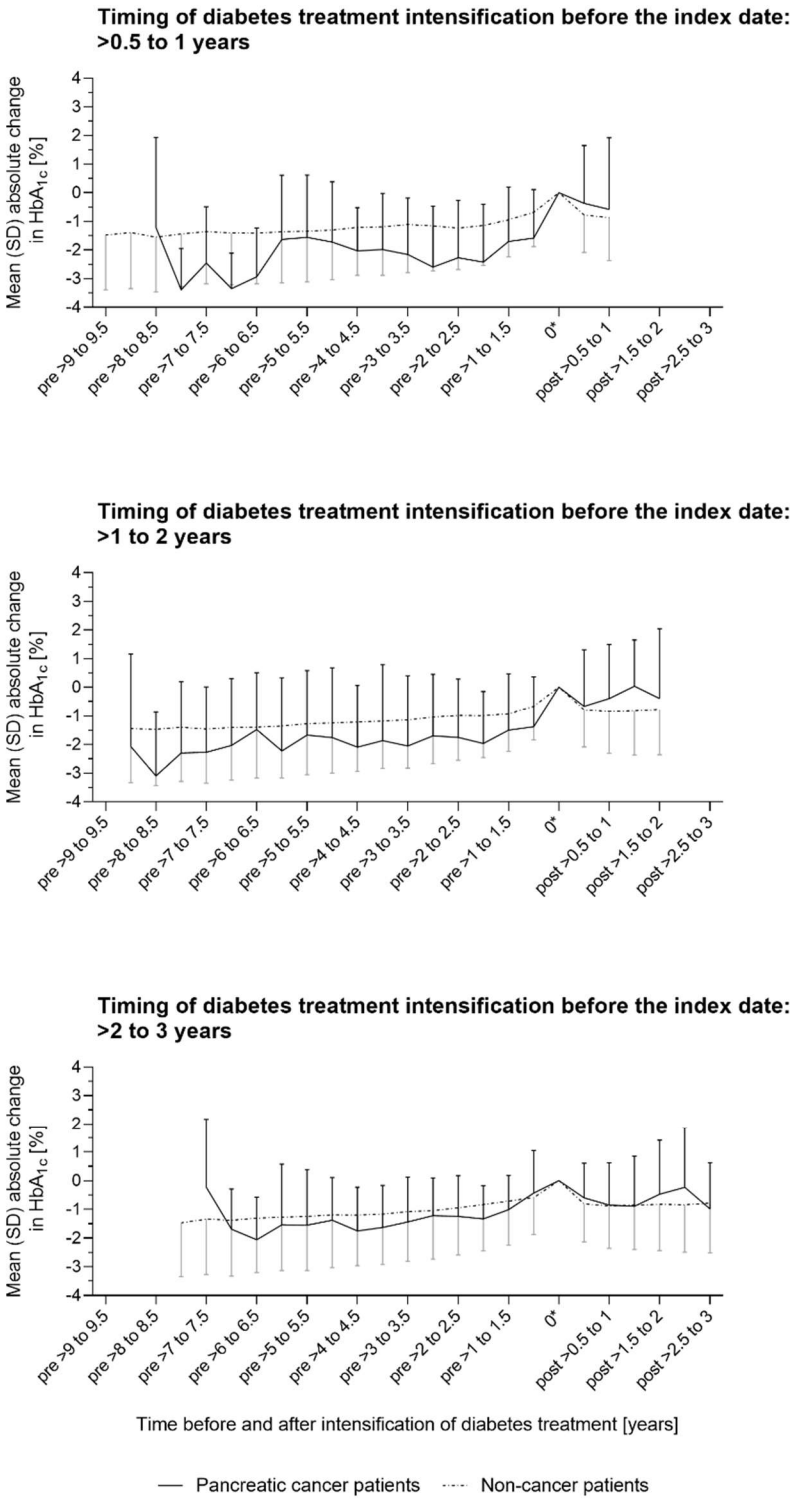
	Pancreatic cancer patients				**Non-cancer patients**			
	Timing of diabetes treatment intensification before the index date [years]			**Overall**	**Timing of diabetes treatment intensification before the index date [years]**			**Overall**
	>2 to 3	**>1 to 2**	**>0.5 to 1**		**>2 to 3**	**>1 to 2**	**>0.5 to 1**	
Relative change in body weight from >2 to 5 years before diabetes treatment intensification to the time of treatment intensification[a,b,c] [%]								
	N = 72	N = 72	N = 31	N = 175	N = 17,930	N = 15,155	N = 6,569	N = 39,654
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
None or gain	29 (40.3)	24 (33.3)	5 (16.1)	58 (33.1)	9,110 (50.8)	7,721 (51.0)	3,339 (50.8)	20,170 (50.9)
Loss:								
0.1-6.0	32 (44.4)	29 (40.3)	11 (35.5)	72 (41.1)	6,420 (35.8)	5,615 (37.1)	2,452 (37.3)	14,487 (36.5)
≥ 6.1	11 (15.3)	19 (26.4)	15 (48.4)	45 (25.7)	2,400 (13.4)	1,819 (12.0)	778 (11.8)	4,997 (12.6)
In all patients with diabetes deterioration								
Mean ± SD	-1.5 ± 8.0	-2.0 ± 8.2	-6.0 ± 7.0	-2.5 ± 8.0	0.2 ± 6.6	0.2 ± 6.3	0.2 ± 6.1	0.2 ± 6.4
Median (IQR)	-1.6 (-4.3;2.9)	-1.5 (-6.2;0.9)	-5.6 (-11.8;-0.3)	-2.1 (-6.1;1.3)	0.0 (-3.4;3.6)	0.0 (-3.2;3.4)	0.0 (-3.2;3.3)	0.0 (-3.3;3.4)
In patients with weight loss of ≥ 6.1%								
Mean ± SD	-15.0 ± 6.9	-11.3 ± 6.0	-11.7 ± 5.1	-12.4 ± 6.0	-10.1 ± 4.5	-9.8 ± 4.3	-9.8 ± 4.2	-9.9 ± 4.4
Median (IQR)	-17.0 (-18.1;-8.5)	-10.1 (-12.7;-7.2)	-11.8 (-14.6;-6.9)	-10.7 (-14.6;-7.6)	-8.7 (-11.4;-7.0)	-8.5 (-11.0;-7.0)	-8.4 (-10.8;-7.0)	-8.6 (-11.2;-7.0)

SD standard deviation; *IQR* interquartile range

[a] The analysis included all patients with at least 1 body weight measurement for each of the 2 time windows. If patients had more than 1 body weight measurement recorded within a time window, we calculated the mean of all available body weight recordings.

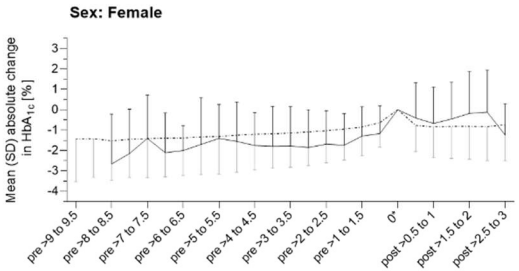
[b] For the definition of categorical cut-offs, we grouped body weight increases and decreases into categories of 0.5% among pancreatic cancer and non-cancer patients. We merged adjacent categories in case they had a similar frequency ratio of pancreatic cancer patients to non-cancer patients, and kept them separate otherwise.

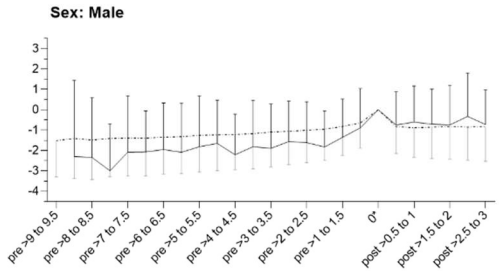
[c] The body weight at treatment intensification was the patient's (mean) weight in the 6 months before the date of diabetes treatment intensification.

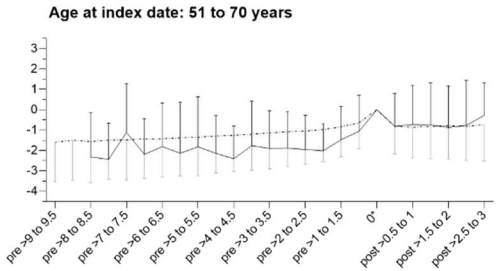


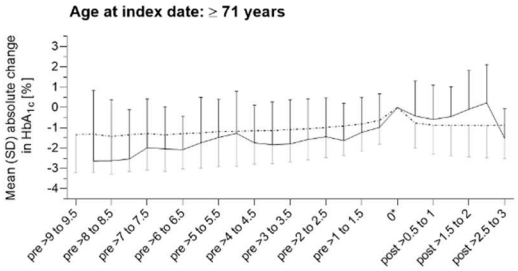
Supplemental Figure 3.3-1. Mean absolute change in HbA_{1c} from diabetes treatment intensification at each of the 6-month intervals before and after intensification in pancreatic cancer patients and non-cancer patients, stratified by timing of diabetes treatment intensification before the index date
*The HbA_{1c} at diabetes treatment intensification was the patient's (mean) HbA_{1c} in the 6 months before the date of intensification.

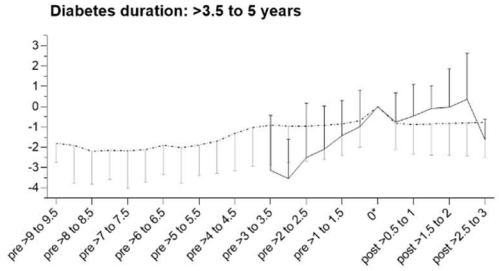
The minimum number of data points required to calculate mean absolute HbA_{1c} change for a time interval was set to 5. *HbA_{1c}* glycated hemoglobin; *SD* standard deviation

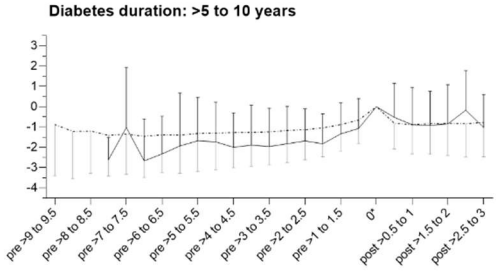

Sex: Female
Mean (SD) absolute change in HbA1c [%]
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

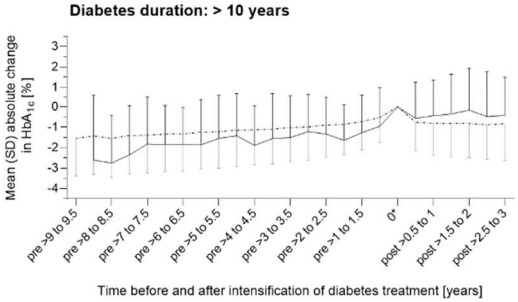

Sex: Male
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

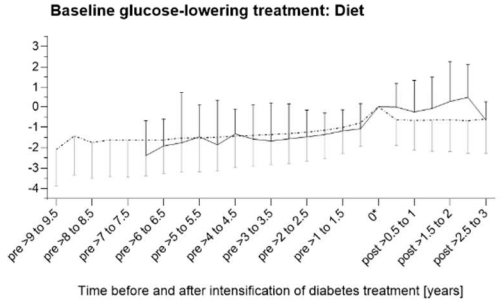

Age at index date: 51 to 70 years
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

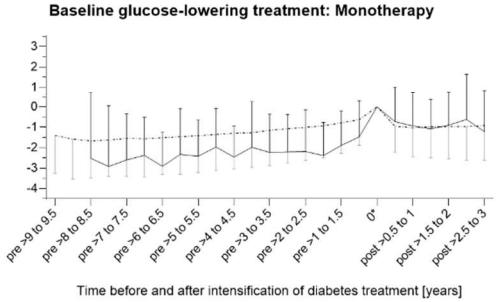

Age at index date: ≥ 71 years
Mean (SD) absolute change in HbA1c [%]
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

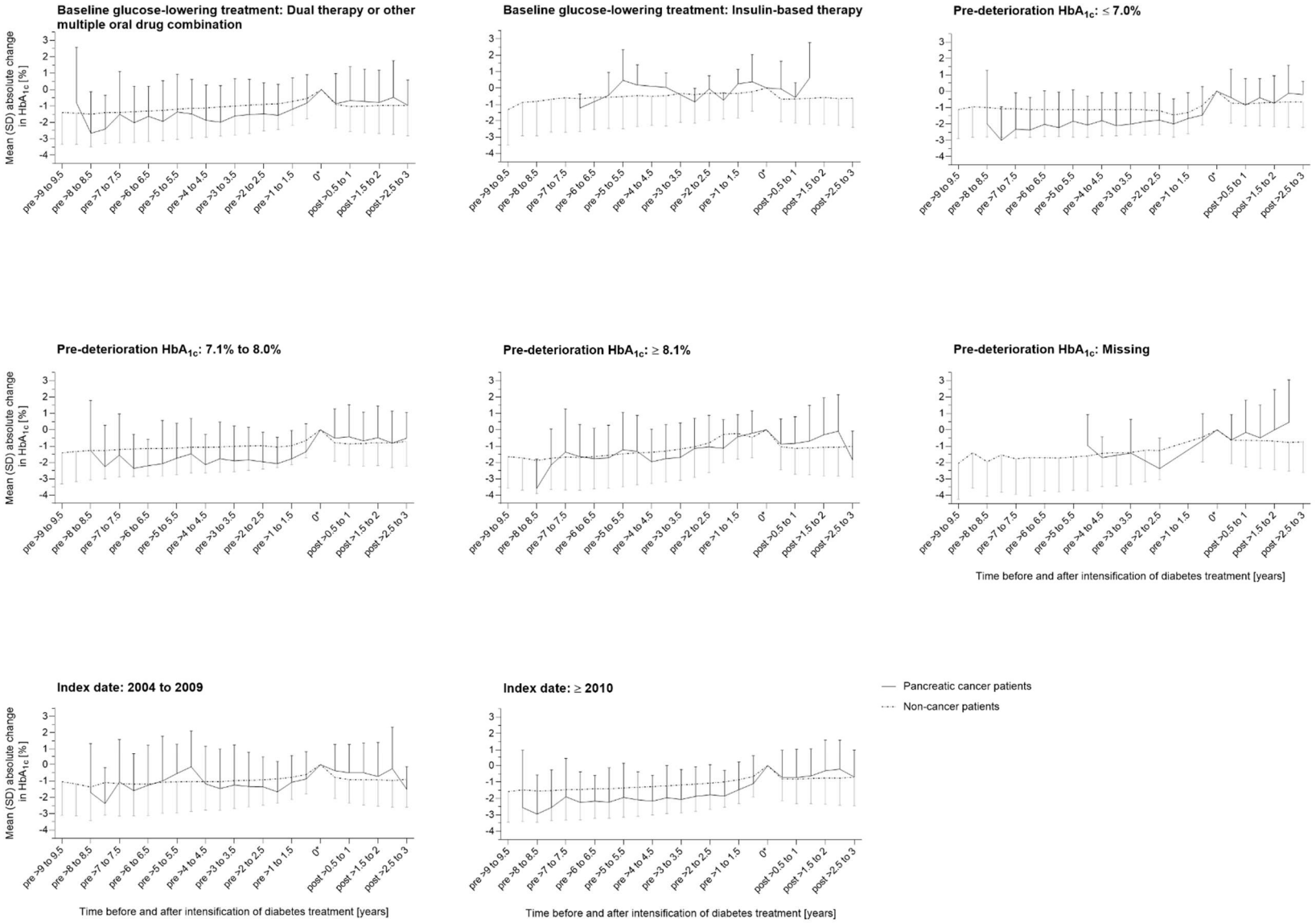

Diabetes duration: >3.5 to 5 years
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3


Diabetes duration: >5 to 10 years
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3


Diabetes duration: > 10 years
Mean (SD) absolute change in HbA1c [%]
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]


Baseline glucose-lowering treatment: Diet
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]

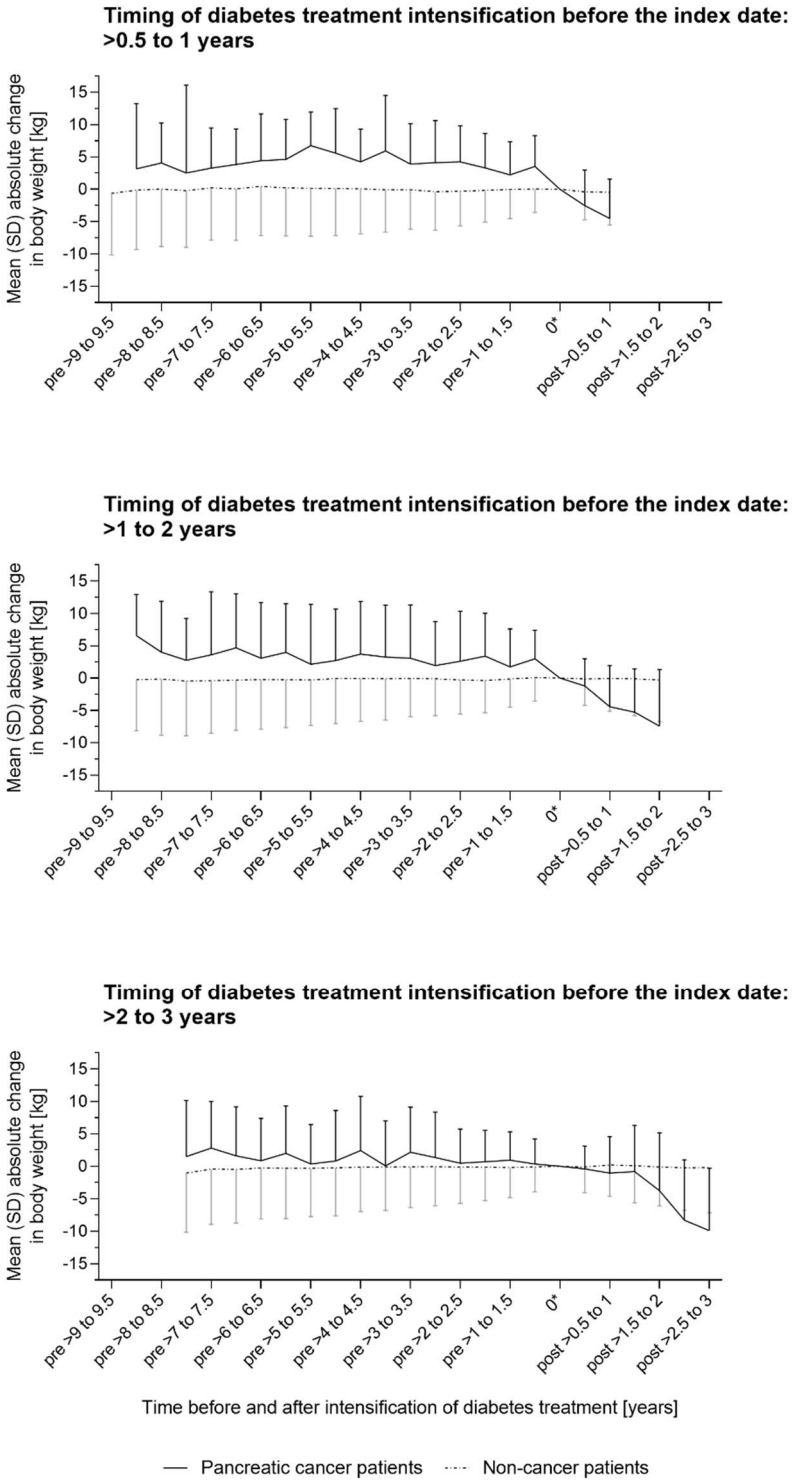

Baseline glucose-lowering treatment: Monotherapy
3
2
1
0
-1
-2
-3
-4
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]


Baseline glucose-lowering treatment: Dual therapy or other multiple oral drug combination
Baseline glucose-lowering treatment: Insulin-based therapy
Pre-deterioration HbA1c: ≤ 7.0%
Pre-deterioration HbA1c: 7.1% to 8.0%
Pre-deterioration HbA1c: ≥ 8.1%
Pre-deterioration HbA1c: Missing
Index date: 2004 to 2009
Index date: ≥ 2010
Mean (SD) absolute change in HbA1c [%]
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0*
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]
Pancreatic cancer patients
Non-cancer patients

Supplemental Figure 3.3-2. Mean absolute change in HbA_{1c} from diabetes treatment intensification at each of the 6-month intervals before and after intensification in pancreatic cancer patients and non-cancer patients, stratified by patient characteristics and index date

*The HbA_{1c} at diabetes treatment intensification was the patient's (mean) HbA_{1c} in the 6 months before the date of intensification.

The minimum number of data points required to calculate mean absolute HbA_{1c} change for a time interval was set to 5. *HbA_{1c}* glycated hemoglobin; *SD* standard deviation

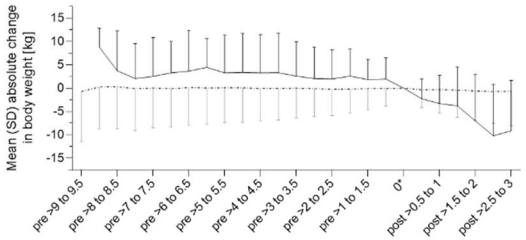


Supplemental Figure 3.3-3. Mean absolute change in body weight from diabetes treatment intensification at each of the 6-month intervals before and after intensification in pancreatic cancer patients and non-cancer patients, stratified by timing of diabetes treatment intensification before the index date

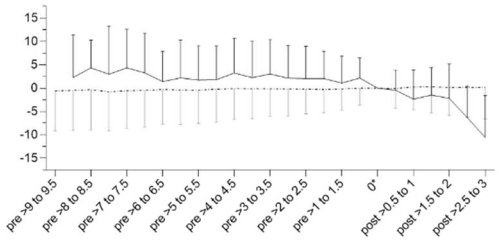
*The body weight at diabetes treatment intensification was the patient's (mean) body weight in the 6 months before the date of intensification.

The minimum number of data points required to calculate mean absolute weight change for a time interval was set to 5. *SD* standard deviation

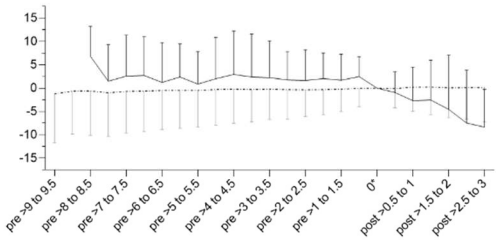
Female



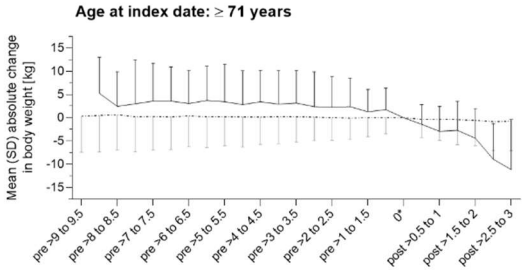
Male



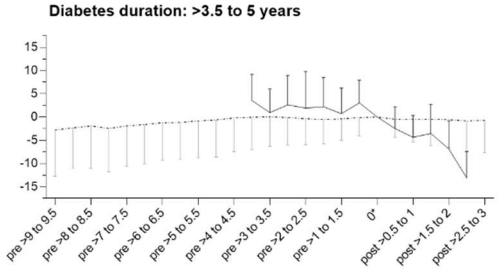
Age at index date: 51 to 70 years



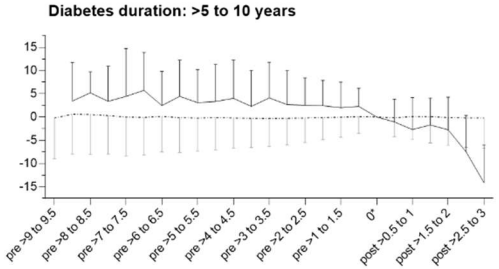
Age at index date: ≥ 71 years



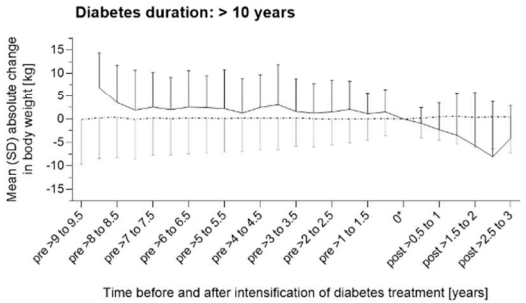
Diabetes duration: >3.5 to 5 years



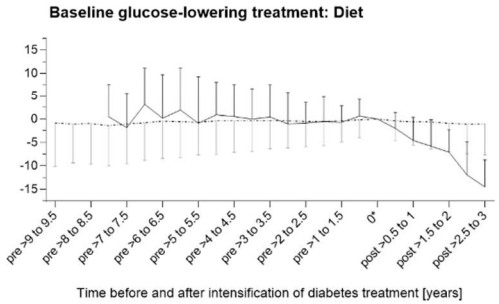
Diabetes duration: >5 to 10 years



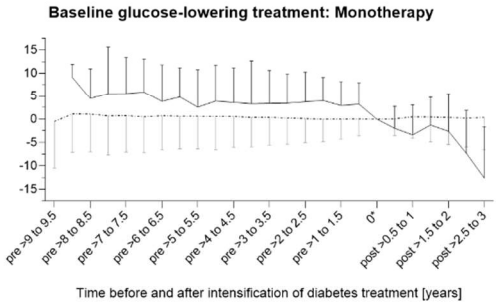
Diabetes duration: > 10 years

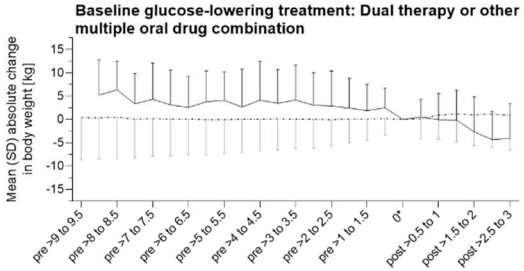


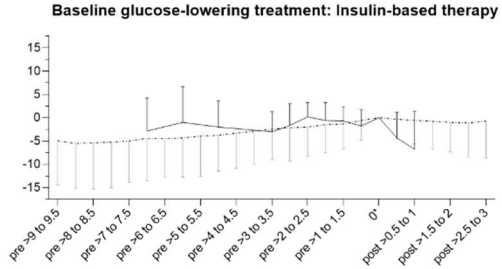
Baseline glucose-lowering treatment: Diet

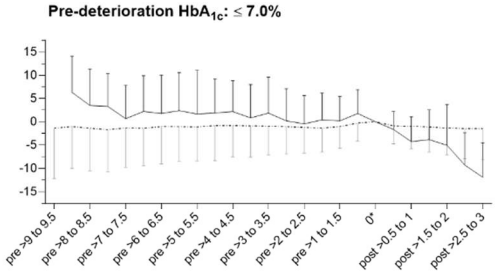


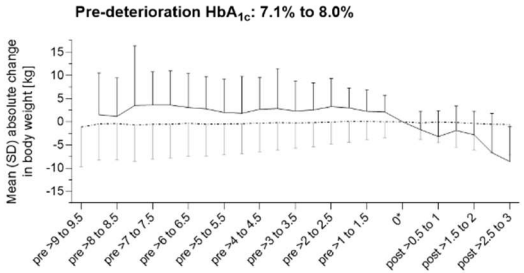
Baseline glucose-lowering treatment: Monotherapy

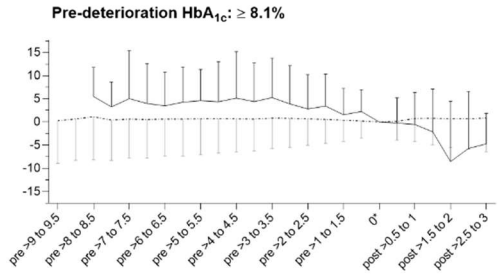


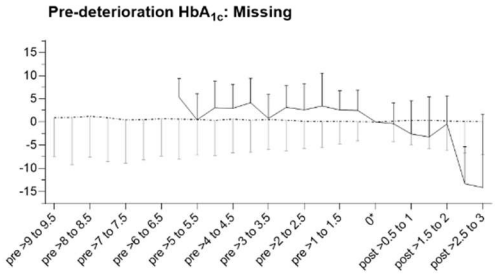

Baseline glucose-lowering treatment: Dual therapy or other multiple oral drug combination
Mean (SD) absolute change in body weight [kg]
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

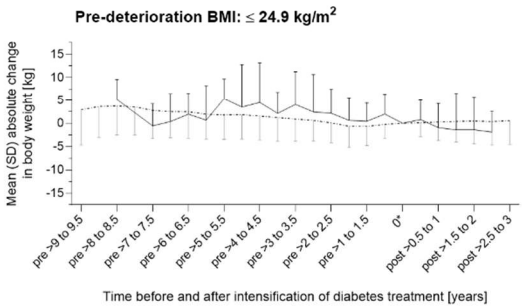

Baseline glucose-lowering treatment: Insulin-based therapy
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

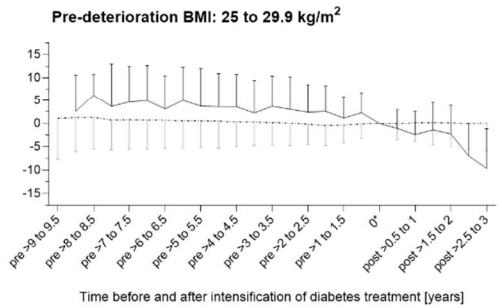

Pre-deterioration HbA1c: ≤ 7.0%
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

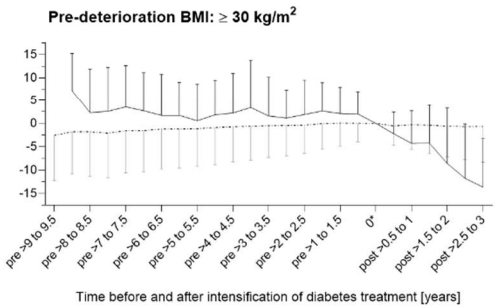

Pre-deterioration HbA1c: 7.1% to 8.0%
Mean (SD) absolute change in body weight [kg]
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3

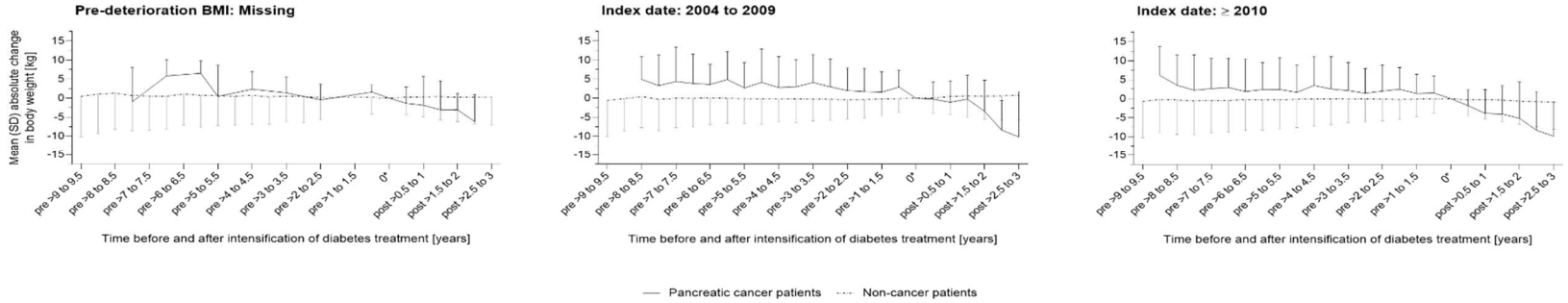

Pre-deterioration HbA1c: ≥ 8.1%
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3


Pre-deterioration HbA1c: Missing
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3


Pre-deterioration BMI: ≤ 24.9 kg/m2
Mean (SD) absolute change in body weight [kg]
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]


Pre-deterioration BMI: 25 to 29.9 kg/m2
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]


Pre-deterioration BMI: ≥ 30 kg/m2
15
10
5
0
-5
-10
-15
pre >9 to 9.5
pre >8 to 8.5
pre >7 to 7.5
pre >6 to 6.5
pre >5 to 5.5
pre >4 to 4.5
pre >3 to 3.5
pre >2 to 2.5
pre >1 to 1.5
0'
post >0.5 to 1
post >1.5 to 2
post >2.5 to 3
Time before and after intensification of diabetes treatment [years]



Supplemental Figure 3.3-4. Mean absolute change in body weight from diabetes treatment intensification at each of the 6-month intervals before and after intensification in pancreatic cancer patients and non-cancer patients, stratified by patient characteristics and index date

*The body weight at diabetes treatment intensification was the patient's (mean) body weight in the 6 months before the date of intensification.

The minimum number of data points required to calculate mean absolute weight change for a time interval was set to 5. *SD* standard deviation

Chapter 4

Discussion and outlook

4 Discussion and outlook

4.1 Discussion

Early detection of pancreatic cancer is a challenging task. Before any real-life impact can be expected, different elements need to be addressed including identification of populations at risk, technological development of assays as well as conduct of clinical trials and cost-benefit analyses.[34] This thesis aimed to contribute to the identification of populations at risk. Specifically, patients with new-onset diabetes mellitus or long-standing diabetes mellitus were studied for further risk stratification in order to establish groups eligible for a screening approach, thereby contributing to the difficult task of disease detection at an early stage (i.e. when patients are still free from subjective complaints). A detailed discussion of the results and limitations of each individual study has been presented in the previous sections. In the following paragraphs, emphasis will be placed on discussing the results in the context of the current scientific environment and transferability to the clinical setting.

4.1.1 Study 3.1

Weight change and blood glucose concentration as markers for pancreatic cancer in subjects with new-onset diabetes mellitus: A matched case-control study[120]

- This was the first large study outside the Rochester Epidemiology Project (Minnesota, US) that evaluated weight loss at the time of diabetes onset as a clinical indicator for pancreatic cancer-associated diabetes.
- Pancreatic cancer patients revealed significantly higher adjusted odds ratios (aORs) for weight loss at diabetes onset than non-cancer patients.
- The magnitude of body weight loss was associated with the disease risk, yielding aORs of 3.5 to 4.5 in patients with weight loss of ≥ 10%. On the other hand, only patients with modest weight loss (i.e. 3.1%-9.9%) seemed to have diabetes onset > 6 months before the cancer diagnosis.
- Absence of pre-diabetes in the years preceding diabetes diagnosis was associated with an around 2-fold increased risk of pancreatic cancer.

A large retrospective cohort study recently suggested that the number needed to screen during a 3-year period to detect 1 pancreatic cancer (assuming a perfect test sensitivity of 100%) amounts to 270 in subjects with new onset of diabetes.[121] This number is considered too high to promote pancreatic cancer screening for new-onset diabetes individuals given that available

screening tests are cost-intensive, partly invasive, and may lead to overdiagnosis and unnecessary treatment in a relevant number of subjects.[15,34,121] Thus, markers for pancreatic cancer to further enrich the new-onset diabetes cohort for the cancer are needed.[34]

In the last few years, there is accumulating evidence that weight loss at the onset of diabetes may serve a clinical indicator of pancreatic cancer.[66,79,115,122] Accordingly, our study (study 3.1) showed that pancreatic cancer patients have a higher risk of weight loss, i.e. change in body weight of > 3% at the time of diabetes onset, than non-cancer patients. Unlike other studies, we further stratified our analyses by the magnitude of weight loss. We found that weight loss of ≥ 10% was associated with a 2- to 3-fold higher risk of pancreatic cancer than weight loss of 3.1% to 9.9%. At the same time, we observed that cancer patients with severe body weight loss generally had diabetes onset only within the last 6 months before the clinical cancer diagnosis, whereas in cancer patients with body weight loss of 3.1% to 9.9%, diabetes was diagnosed > 6 months ahead of the cancer diagnosis and, thus, at a time when tumors may still be resectable.[75] As such, findings from our study suggest that only modest body weight loss may serve as a – yet limited – marker for early pancreatic cancer in subjects with new-onset diabetes.

Weight loss prior to the onset of other cancer-specific symptoms (i.e. > 6 months) is a recognized paraneoplastic phenomenon induced by the tumor.[47] A recent study reported that the decreases in body weight result from loss in abdominal subcutaneous adipose tissue.[123] In contrast, weight loss within the last 6 months prior to the pancreatic cancer diagnosis is attributed to cachexia including additional loss of muscle and visceral adipose tissue.[123] Thus, it appears reasonable to claim that the magnitude of weight loss associated with diabetes correlates with the timing of diabetes prior to the clinical diagnosis.

Different from type 2 diabetes, pancreatic cancer-associated diabetes is of rapid onset.[68] Whether the absence of pre-diabetes prior to diabetes onset may serve as a useful indicator for pancreatic cancer has not been investigated though. Within study 3.1, we showed that non-elevated blood glucose levels (≤ 5.6 mmol/L) in the years leading up to diabetes onset were associated with a 2-fold higher risk for a subsequent pancreatic cancer diagnosis than elevated blood glucose levels. Yet, we further found that the absence of pre-diabetes may be a particular feature of pancreatic cancer patients with diabetes onset close to the clinical cancer diagnosis, and thus, may be of limited help in the early detection of pancreatic cancer. However, further studies on the association between blood glucose patterns and the risk of pancreatic cancer in patients with new onset of diabetes appear warranted.

In the last years, different prediction models to determine the pancreatic cancer risk in new-onset diabetes subjects have been developed.[79,94,124] Most attention attracted the model

termed the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model.[79] This model scores patients according to three variables, consisting of age at diabetes as well as body weight change and change in blood glucose, both in the year before the diabetes diagnosis. Out of the three variables, body weight change is weighed the most. Scores will be higher the older a patient is, the more body weight the patient loses, and the higher the increase in blood glucose prior to the diabetes onset is. Based on the calculated total score, patients' pancreatic cancer risk is classified either as high, intermediate, or low. Until further results of an ongoing prospective trial are available,[125] it remains questionable whether early diagnosis of pancreatic cancer can reliably be made by applying a model that heavily relies on body weight changes. More so as results from our study (study 3.1) suggest that serious changes in body weight occur late in the course of the disease.

4.1.2 Study 3.2

The potential of glycemic control and body weight change as early markers for pancreatic cancer in patients with long-standing diabetes mellitus – A case-control study[86]

- Among subjects with long-standing type 2 diabetes mellitus, duration of insulin treatment was inversely associated with the risk of pancreatic cancer.
- Glycated hemoglobin (HbA_{1c}) values of ≥ 8% were associated with an increased risk of pancreatic cancer in the >4 to 5 years before the cancer diagnosis. The association between HbA_{1c} values of ≥ 8% and pancreatic cancer risk became stronger with closer proximity to the cancer diagnosis, in particular in the >2 to 3 years before the clinical diagnosis.
- Absolute and relative loss in body weight from 3 years before the pancreatic cancer diagnosis up to the time of cancer diagnosis was associated with an increased risk of pancreatic cancer, with the aORs increasing with increasing weight loss.

Review articles on the relationship between diabetes and pancreatic cancer consistently describe the association between the two diseases as complex.[126–129] They argue that diabetes can be both a risk factor and a consequence of pancreatic cancer. And indeed, long-standing type 2 diabetes increases the risk of developing pancreatic cancer approximately 2 times[50,102,103] by mechanisms that have yet to be elucidated but may involve hyperinsulinemia, inflammation, and hyperglycemia,[106,130] while pancreatic tumors can provoke secondary diabetes through the secretion of yet to be identified diabetogenic mediator(s).[48] However, the association between diabetes and pancreatic cancer is even more complex than

that. Specifically, pancreatic tumors do not only manifest as new-onset diabetes but also as diabetes deterioration in long-standing type 2 diabetes patients, which is highlighted by findings of an increased risk of pancreatic cancer in type 2 diabetes patients with short-term use of insulin.[69,131] Because a) diabetes deterioration represents the counterpart manifestation of new-onset diabetes in patients with pre-existing abnormalities in glucose metabolism and b) new onset of diabetes has been characterized as an early harbinger of pancreatic cancer and identified as a potential key to early disease detection,[132] dedicated research on the occurrence of diabetes deterioration in association with pancreatic cancer is warranted.

At this point, study 3.2 comes into play, which provided conclusive evidence that diabetes deterioration occurs early before the clinical detection of pancreatic cancer. In particular from >2 to 3 years before the diagnosis of pancreatic cancer up to the time of cancer diagnosis, poor diabetes control (HbA_{1c} ≥ 8%) was associated with a distinctly increasing pancreatic cancer risk.

Results from study 3.2 are complemented by a recent trial, which studied the impact of diabetes deterioration as a diagnostic possibility on the prognosis of pancreatic cancer patients.[55] The early diagnosis of pancreatic cancer in association with diabetes deterioration in still asymptomatic patients was associated with smaller tumors, earlier disease stage, and higher resectability rates than in symptomatic patients. This translated into an improved survival rate when compared with patients who were diagnosed based on cancer-related symptoms.[55]

Studies in basic science ideally spark future investigations, which will follow up on the reported outcomes. Our data will hopefully do so, i.e. will trigger further research on the role of diabetes deterioration in the context of early pancreatic cancer detection – something that has not been achieved by one previous study that reported on increasing blood glucose levels among diabetic pancreatic cancer patients in the years before the cancer diagnosis.[68] The limited interest – and maybe confidence – in the prior observation may be explained by the fact that it a) was obtained from a sub-analysis conducted in a small number of pancreatic cancer patients and b) attained little attention in the published manuscript.

4.1.3 Study 3.3

Characterization of the deterioration of diabetes control in patients with a subsequent diagnosis of pancreatic cancer: A descriptive study

- HbA_{1c} and body weight changes in pancreatic cancer patients with diabetes deterioration in the >0.5 to 3 years prior to the clinical diagnosis differed from those in non-cancer patients with type 2 diabetes deterioration. Specifically,
    - the mean absolute increase in HbA_{1c} from the pre-deterioration period, i.e. the time >1 to 2 years before diabetes treatment intensification, to the time of treatment intensification, was 1.5% ± 1.6% in pancreatic cancer patients vs. 0.9% ± 1.4% in non-cancer patients.
    - the mean absolute HbA_{1c} difference between the pre-deterioration period and the 6-month interval after diabetes treatment intensification was 0.9% ± 1.8% in pancreatic cancer patients compared with 0.1% ± 1.5% in non-cancer patients.
    - from the pre-deterioration period to the time of intensification of diabetes treatment, body weight decreased, on average, by 1.9% ± 6.4% in cancer patients, whereas in non-cancer patients, body weight increased, on average, by 0.3% ± 5.2%.

How do HbA_{1c} and body weight changes in subjects with pancreatic cancer-associated diabetes deterioration compare with those in non-cancer patients with type 2 diabetes progression? – This was the research question of a follow-up study of study 3.2. The study results should provide information about whether HbA_{1c} and body weight may be of use for the further pancreatic cancer risk stratification among patients with diabetes deterioration. Needless to say, other research questions, for example, on the exact number of pancreatic cancer patients developing diabetes deterioration prior to the clinical diagnosis would have been equally worth to study. However, findings and issues observed in our own prior study (study 3.2) as well as the evaluation of randomly selected profiles of diabetic pancreatic cancer patients decisively affected - as this is often the case[133] - the focus of the study. More specifically, in study 3.2, we found that weight loss in the 3 years before the pancreatic cancer diagnosis was associated with an elevated risk for pancreatic cancer patients. However, because we did not assess the time of occurrence of weight loss prior to the cancer diagnosis, we were unable to conclude whether pancreatic cancer patients already lose body weight at the time of diabetes deterioration or only in the presence of cachexia, shortly before the clinical

diagnosis. Remarkably high increases in HbA_{1c} at the time of diabetes deterioration attracted our attention in the electronic health records of diabetic pancreatic cancer patients and called for further quantitative work-up at the population level.

Study 3.3 revealed intriguing results, suggesting that steep increases in HbA_{1c} and loss in body weight occur distinctly more often in association with pancreatic cancer-associated diabetes deterioration than with type 2 diabetes progression. We found that persistent elevation of HbA_{1c} after diabetes treatment intensification may be a characteristic feature of pancreatic cancer-associated diabetes deterioration. Findings may particularly apply to pancreatic cancer patients with diabetes deterioration within the 2 years before cancer diagnosis. Stratification of study results by demographics and clinical characteristics allowed to rule out that imbalances in the baseline characteristics of pancreatic cancer and non-cancer patients led to the observed differences between patient groups.

Pancreatic cancer screening is currently considered to be applicable in patient cohorts with a 3-year incidence of pancreatic cancer of at least 3% to 4%.[34] In patient cohorts with a lower pancreatic cancer risk, risk stratification should be conducted, to enrich the population for the disease. Data on the 3-year risk of pancreatic cancer among patients with diabetes deterioration do not exist. However, given the current study findings, it is possible to roughly assess the latter and, in particular, to put it into perspective with the declared target level (3%-4%) and the corresponding risk in subjects with new-onset diabetes. Calculations look as follows and were performed using UK-based diabetes data (as an example):

(a) In the UK, 2.9 million patients aged 50 years or older have type 2 diabetes.[134,135] Based on our results, 14% of these have diabetes deterioration every year i.e. 406,000 subjects (in study 3.3, 35% had diabetes deterioration in the >0.5 to 3 years before the index date).

(b) In the UK, approximately 10,500 patients are annually diagnosed with pancreatic cancer.[116] Of these, 1575 (15%) have pre-existing diabetes.[86] Based on our results, 18% of them have diabetes deterioration in each of the 3 years before cancer diagnosis, i.e. 852 subjects in total and 284 subjects per year (in study 3.3: 44% had diabetes deterioration in the >0.5 to 3 years before the cancer diagnosis; linear correlation was assumed [for simplification] to calculate the corresponding proportion for the time window 0-3 years).

(a+b) According to the calculations under a and b, a UK-cohort X, which includes all subjects with diabetes deterioration in year X, encompasses 406,852 subjects; 406,000 subjects, of whom no one will develop pancreatic cancer in the subsequent 3 years + 3 x 284 subjects, of whom one-third will develop pancreatic cancer in year X+1, one-third in year X+2, and another third in year X+3. As such, the 3-year incidence of pancreatic cancer among subjects with diabetes deterioration will approximately amount to 0.2%. For comparison, the corresponding

3-year incidence among new-onset diabetes subjects is around 1%.[46] Thus, expanded intensive risk stratification will be necessary to establish an eligible screening population of subjects with diabetes deterioration. HbA_{1c} and body weight change may play a relevant role in this risk assessment process, but specific biomarkers for pancreatic cancer will probably be needed.

4.1.4 Conclusions

Early detection of pancreatic cancer is the key to sustainably reducing pancreatic cancer mortality. Specifically, to enable surgical resection of the tumor, pancreatic cancer has to be detected in subjects still free of subjective complaints, i.e. by means of screening.

This thesis aimed to contribute to the establishment of groups within the diabetes mellitus population that are eligible for pancreatic cancer screening. Specifically, this thesis aimed to evaluate whether body weight change and glycemic control can help to enrich the cohorts of new-onset diabetes subjects and long-standing diabetes subjects for pancreatic cancer.

In subjects with new-onset diabetes, moderate weight loss at the time of diabetes onset may serve as an early, yet limited, marker for pancreatic cancer. Severe weight loss and blood glucose levels in the normal range (i.e. absence of pre-diabetes) before the onset of diabetes were also found to be predictive of pancreatic cancer-associated diabetes, yet may occur too late in the course of the disease to help the cancer prognosis. In subjects with long-standing diabetes, poor glycemic control ($HbA_{1c} \geq 8\%$) was found to be associated with an elevated risk of pancreatic cancer. More importantly, findings on an increasing association between poor glycemic control and pancreatic cancer risk in the >4 to 5 years before the cancer detection demonstrated that worsening of diabetes may be an early harbinger of pancreatic cancer. To become a useful clinical indicator for pancreatic cancer, pancreatic cancer-associated diabetes deterioration needs to be distinguishable from typical diabetes mellitus type 2 progression. The study in pancreatic cancer and non-cancer subjects with diabetes deterioration revealed that pancreatic cancer-associated deterioration of diabetes control may frequently be characterized by pronounced increases in HbA_{1c}, persistent elevation of HbA_{1c} after treatment intensification, and concomitant weight loss. In summary, body weight change and glycemic control can help advancing risk stratification within the diabetic population and thus may contribute to an early detection of pancreatic cancer. However, specific biomarkers would be desirable.

4.2 Outlook

Early detection of pancreatic tumors is and will remain the key to sustainably reducing pancreatic cancer mortality. The challenges of early detection are tremendous though. Easy and rapid solutions cannot be expected. And yet, novel strategies and tools with the potential to revolutionize early detection of pancreatic cancer are currently being investigated or even already tested in the clinical setting. In the following, research that may move early pancreatic cancer detection forward in subjects with new-onset diabetes and in those with diabetes deterioration is highlighted:

Early Detection Initiative for Pancreatic Cancer I The Early Detection Initiative for Pancreatic Cancer is a multi-center randomized controlled trial that is designed to evaluate if algorithm-based screening in patients with new-onset diabetes leads to earlier detection of pancreatic cancer.[125] The algorithm applied for the selection of subjects undergoing computed tomography or MRI imaging screening is based on the ENDPAC model.[79] As reported in the context of study 3.1, this model uses three clinical parameters – change in body weight, change in blood glucose, and age at onset of diabetes – to calculate a person's pancreatic cancer risk. Based on our findings in study 3.1, concerns have been raised that the combination of these parameters may not be ideal to particularly identify subjects with pancreatic cancer-associated diabetes early in the course of the disease. Results from this ongoing prospective trial will clarify whether or not our concerns are justified. More importantly, findings from this clinical trial will provide detailed information on the possibilities (and barriers) related to establishing screening for sporadic pancreatic cancer in subjects with new-onset diabetes. Study results will be available in 2030 at the earliest.[125]

New-onset diabetes cohort I The Consortium for the study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC), which is a research program initiated by the National Cancer Institute (NCI) and the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK), has launched a project to establish a biobank of clinically annotated biospecimens from (a) pre-symptomatic pancreatic cancer patients with new onset of diabetes and (b) new-onset type 2 diabetes control subjects.[95] As many as 10,000 Americans aged 50 years or older with newly diagnosed diabetes are currently included in a cohort, called the new-onset diabetes cohort. All subjects enrolled will be followed up for the development of pancreatic cancer over the next 3 years and for the collection of biospecimen samples at the time of recruitment, and subsequently at 6, 12, and 24 months.[136] The previous shortage of biological samples adequately linked to clinical data and serially collected in subjects eventually

diagnosed with pancreatic cancer is considered to be one major limitation in the development and validation of biomarkers for the early detection of the disease.[15] By implementing the new-onset diabetes cohort, CPDPC aims to speed up the validation of promising biomarkers or biomarker panels, which will help in further enriching the high-risk group of new-onset diabetes subjects for pancreatic cancer, but which may be similarly useful for the risk stratification in other populations, for example in subjects with deteriorating diabetes.

Chapter 5

Appendix

5 Appendix

5.1 Additional study

5.1.1 The risk of muscular events among new users of hydrophilic and lipophilic statins

An observational cohort study

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Abstract

Background: Statins are effective lipid-lowering drugs for the prevention of cardiovascular disease, but muscular adverse events can limit their use. Hydrophilic statins (pravastatin, rosuvastatin) may cause less muscular events than lipophilic statins (e.g. simvastatin, atorvastatin) due to lower passive diffusion into muscle cells.

Objective: To compare the risk of muscular events between statins at comparable lipid-lowering doses and to evaluate if hydrophilic statins are associated with a lower muscular risk than lipophilic statins.

Design/Setting: Propensity score-matched cohort study using data from the United Kingdom-based Clinical Practice Research Datalink (CPRD) GOLD.

Patients: New statin users. Cohort 1: pravastatin 20-40 mg (hydrophilic) vs simvastatin 10-20 mg (lipophilic), cohort 2: rosuvastatin 5-40 mg (hydrophilic) vs atorvastatin 10-80 mg (lipophilic), and cohort 3: simvastatin 40-80 mg vs atorvastatin 10-20 mg.

Main measures: The outcome was a first record of a muscular event (myopathy, myalgia, myositis, rhabdomyolysis) during a maximum follow-up of one year.

Key results: The propensity score-matched cohorts consisted of 1) 9,703, 2) 7,032, and 3) 37,743 pairs of statin users. Comparing the risk of muscular events between low-intensity pravastatin vs low-intensity simvastatin yielded a HR of 0.86 (95% CI 0.64-1.16). In the comparison of moderate- to high-intensity rosuvastatin vs equivalent doses of atorvastatin, we observed a HR of 1.17 (95% CI 0.88-1.56). Moderate- to high-intensity simvastatin was associated with a HR of 1.33 (95% CI 1.16-1.53), when compared with atorvastatin at equivalent doses.

Limitations: We could not conduct other pairwise comparisons of statins due to small sample size. In the absence of a uniform definition on the comparability of statin doses, the applied dose ratios may not fully match with all literature sources.

Conclusions: Our results do not suggest a systematically lower risk of muscular events for hydrophilic statins when compared to lipophilic statins at comparable lipid-lowering doses.

Introduction

Statins are effective lipid-lowering drugs for the primary and secondary prevention of ischemic cardiovascular events.[1,2] Although generally well tolerated, statins may cause myalgia, and less frequently myositis or rhabdomyolysis.[3] According to randomized controlled trials (RCTs), 1.5%-5.0% of patients experience adverse muscular symptoms during statin treatment.[4] However, observational studies suggested that in routine care up to 10%-15% of statin users experience such adverse events.[2,4]

The myotoxicity of statins appears to be dose-dependent and may differ across individual statins,[5,6] as suggested by the market withdrawal of cerivastatin due to its pronounced risk of rhabdomyolysis.[7] It has been hypothesized that hydrophilic / water-soluble statins (i.e. rosuvastatin and pravastatin) are less likely to cause muscular side effects than lipophilic / fat-soluble statins (e.g. simvastatin or atorvastatin) due to lower passive diffusion into muscle cells.[8,9] This hypothesis is supported by *in vitro* data showing a higher cytotoxicity on C2C12 myotubes for lipophilic statins than hydrophilic statins.[10]

Results from RCTs, however, suggest a similar muscular risk for hydrophilic and lipophilic statins at comparable lipid-lowering doses, but the absolute numbers of events in these trials were low.[11,12] A more comprehensive and robust description of the comparative muscular risk of statins at equivalent doses is needed to improve our understanding of the role of statin choice for the risk of such adverse events.

We aimed to assess the risk of muscular events between statins at comparable lipid-lowering doses, and to evaluate if hydrophilic statins are associated with a systematically lower risk of muscular events than lipophilic statins.

Methods

Study design and data resource

We conducted an observational cohort study using data from the United Kingdom-based Clinical Practice Research Datalink (CPRD) GOLD. CPRD GOLD is a primary care database[13] that contains anonymized longitudinal electronic medical records on more than 15 million patients.[14,15] The data held in the CPRD GOLD are collected in general practices as part of routine care.[15] Data on demographics, medical diagnoses or symptoms (using 'Read codes'), or lifestyle factors are available. CPRD GOLD contains comprehensive and detailed information on drug prescriptions, including product name, dose, number of tablets, and prescription date.[15]

The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research (protocol no. 19_052) and has been made available to the journal editors.

Study population

We identified all patients in CPRD GOLD aged 40 to 80 years with a first statin prescription between January 2000 and December 2017. Of these, we selected all patients with a first prescription for hydrophilic pravastatin 20-40 mg, hydrophilic rosuvastatin 5-40 mg, lipophilic atorvastatin 10-80 mg, or lipophilic simvastatin 10-80 mg who did not have any of the following exclusion criteria at the cohort entry date (CED), defined as date of the first statin prescription: I) < 3 years of medical records in CPRD GOLD, II) prior record of rhabdomyolysis, myositis, or myopathy (except myalgia, muscle ache, or muscle pain), III) prior diagnosis of a primary muscle disorder, myoneural disorder, or a disorder associated with muscle pain (e.g. polymyalgia rheumatica, fibromyalgia), and/or IV) any diagnosis of cancer (except non-melanoma skin cancer), alcoholism or other substance abuse, or HIV.

To minimize heterogeneity in patient frailty, we categorized patients into two groups of I) primary or II) secondary prevention of cardiovascular disease. Those with a diagnosis of myocardial infarction or ischemic stroke before the CED were classified as secondary prevention. All others were classified as primary prevention. Within each of the two groups, we established 3 cohorts (6 cohorts in total) to conduct pairwise comparisons of statins at comparable lipid-lowering doses: Cohort 1: new users of pravastatin 20-40 mg vs simvastatin 10-20 mg (low-intensity statin therapy), cohort 2: new users of rosuvastatin 5-40 mg vs atorvastatin 10-80 mg, and cohort 3: new users of simvastatin 40-80 mg vs atorvastatin 10-20 mg (moderate- to high-intensity statin therapy). We could not conduct other pairwise comparisons due to small sample size. We based comparability of doses on national guidelines in the United Kingdom.[1] Because rosuvastatin was only launched in the United Kingdom in March 2003,[16] the CED of atorvastatin users in cohort 2 had to be at or after that date. New users of atorvastatin 10-20 mg may have been included in cohort 2 and 3.

Statin exposure measurement and follow-up

We followed patients in an ‘as treated’ approach from the day after CED for a maximum of one year or until the occurrence of an outcome (muscular event). We censored patients 90 days after statin discontinuation (no prescription re-fill for the study drug within 90 days after the

estimated end date of statin supply[17]), on the day of treatment switch (prescription for a type of statin other than the study drug), death, disenrollment from CPRD GOLD, the day of a recorded exclusion criterion, a recording of statin intolerance (if not classified as outcome, see below), or at the end of the study period (December 31st, 2017). We introduced the 90-day grace period for censoring after statin discontinuation to account for potentially delayed recording of outcomes. We calculated the supply of a statin prescription based on the prescribed number of tablets and on an assumed regimen of one tablet per day.

Study outcomes

The outcome of interest was a muscular event, defined as a recorded Read code for I) myopathy (proximal, drug-induced, or toxic), myalgia (including 'muscle pain' or 'muscle ache'), myositis, rhabdomyolysis, or unspecified muscle disorder, or II) statin intolerance, if followed by a Read code listed under I) within 90 days (N = 32). Read codes are listed in Appendix Table 1.

Covariates

We assessed 42 baseline covariates[7,18-21] before the CED including demographics, lifestyle factors, body mass index, comorbidities, co-medication, health care utilization, and the initially prescribed statin dose (Appendix Table 2).

Statistical analysis

Within each of the 6 cohorts, we performed propensity score (PS) matching, which is an established method to control for confounding by balancing assessed baseline covariates between comparison groups.[22,23] Assessed baseline covariates were potential confounders or predictors of the risk of muscular events.[22] For each patient, we calculated a PS, i.e. the predicted probability of receiving the statin of interest over the comparator statin based on all assessed baseline covariates, using multivariable logistic regression (dependent variable: treatment group; predictor variables: assessed baseline covariates). To account for potential bias due to changes in statin prescribing practice over time,[1,24,25] we calculated calendar time-specific PS, i.e. performed PS calculation separately within 2-year time intervals, each including the patients with a CED during that time period.[26] We matched users of a statin of interest 1:1 to users of a comparator statin with a comparable PS within the 2-year time interval, applying a greedy 5-to-1 digit matching algorithm. This algorithm initially matches on 5 digits

of the PS and, in each iteration, on a further reduced number of digits to match the previously unmatched statin users. Statin users who could not be matched were excluded. It has been shown that treatment groups with the same distribution of propensity scores have the same distribution of all assessed baseline covariates.[27] Covariate balance before and after PS matching was assessed using absolute standardized differences (ASD). We defined covariate balance as an ASD <10%.[28] We plotted Kaplan-Meier curves in the matched cohorts and performed Cox proportional hazard analyses to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). As part of the primary analysis, we calculated time-specific HRs for the follow-up periods of 1 to 30 days, 31 to 90 days, 91 to 180 days, and 181 to 365 days in the primary prevention cohorts.

We performed subgroup analyses by sex, age, and initial daily statin dose and conducted sensitivity analyses restricted to patients with I) no muscle complaints before the CED and II) no use of CYP3A4 inhibiting drugs. CYP3A4-mediated interactions with simvastatin and atorvastatin have been described as a clinically relevant cause of muscular adverse events.[7,29,30] In further analyses, we I) additionally censored for change in statin dose and II) applied a broader outcome definition including all 'statin intolerance' records. Finally, we repeated our analyses as multivariable regression analyses. Appendix Table 3 provides further information on the additionally performed analyses. We conducted the majority of additional analyses only in the primary prevention cohorts due to the small sample size of the secondary prevention cohorts. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Cohort characteristics

We identified 553,178 eligible statin initiators, of which we grouped 469,860 (84.9%) patients into the primary prevention group and 83,318 (15.1%) patients into the secondary prevention group (Appendix Figure 1). In the primary prevention group, we obtained the following PS-matched cohorts: I) 9,703 pairs of pravastatin 20-40 mg vs simvastatin 10-20 mg, II) 7,032 pairs of rosuvastatin 5-40 mg vs atorvastatin 10-80 mg, and III) 37,743 pairs of simvastatin 40-80 mg vs atorvastatin 10-20 mg. The corresponding cohorts in the secondary prevention group included IV) 4,121, V) 836, and VI) 6,716 pairs.

In all 6 cohorts, covariate balance was achieved after PS matching (Table 1, Appendix Tables 4-7; censoring reasons after PS matching in Table 2 and Appendix Table 8). Kaplan

Meier plots for the primary prevention cohorts are displayed in Appendix Figure 2. Sample size, covariate distribution, and censoring reasons for the cohorts before PS matching are shown in the Appendix Tables 4-10.

Comparative Safety

Primary prevention group

Low-intensity statin therapy

Pravastatin (hydrophilic) vs simvastatin (lipophilic)

After PS matching, the incidence rate (IR) of muscular events was 10.8 per 1000 person-years (PYs) in pravastatin users and 12.5 per 1000 PYs in simvastatin users (Table 3). The overall HR for the risk of muscular events was 0.86 (95% CI 0.64-1.16) for pravastatin use compared with simvastatin use, which was driven by low HRs between days 1-30 (HR 0.60, 95% CI 0.26-1.37) and days 31-90 (HR 0.60, 95% CI 0.32-1.11) of follow-up. After day 90, HRs attenuated to a null result (Table 4 and Appendix Figure 3). Results were not meaningfully different within subgroups by age and statin dose. The HR was higher in women (0.99, 95% CI 0.67-1.47) than men (HR 0.73, 95% CI 0.47-1.14). The overall result did not change materially after restriction to statin users without concomitant use of CYP3A4 inhibitors, restriction to patients with no muscle complaints before the CED, and additional censoring for change in statin dose. When we applied the broader outcome definition including all records of ‘statin intolerance’, the HR decreased to 0.70 (95% CI 0.54-0.91) (Table 5). Findings from the multivariable regression analyses were similar to those obtained in the PS-matched cohort (Appendix Table 11).

Moderate- to high-intensity statin therapy

Rosuvastatin (hydrophilic) and simvastatin (lipophilic) vs atorvastatin (lipophilic)

In the PS-matched cohort of rosuvastatin vs atorvastatin, IRs of muscular events were 17.8 and 15.2 per 1000 PYs, and in the PS-matched cohort of simvastatin vs atorvastatin, they were 16.5 and 12.4 per 1000 PYs, respectively (Table 3). The overall HR was 1.17 (95% CI 0.88-1.56) for rosuvastatin compared with atorvastatin and 1.33 (95% CI 1.16-1.53) for simvastatin compared with atorvastatin. In both cohorts, the HR was highest during the first 90 days of follow-up, and attenuated towards the null thereafter. The highest HRs, with atorvastatin as the referent, were 1.43 (95% CI 0.82-2.50) for rosuvastatin between days 31-90 of follow-up,

and 1.91 (95% CI 1.29-2.81) for simvastatin between days 1-30 of follow-up (Table 4 and Appendix Figure 3). Results of subgroup, sensitivity, and additional analyses were not meaningfully different from the overall result in both cohorts (Table 5). Results from the multivariable regression analyses were consistent with the findings obtained in the PS-matched cohorts (Appendix Table 11).

Secondary prevention group

After PS matching, we observed an overall HR of 1.04 (95% CI 0.68-1.59) for pravastatin when compared with simvastatin, which decreased to 0.89 (95% CI 0.61-1.30) after applying the broader outcome definition (Appendix Table 12). In the PS-matched cohorts of rosuvastatin and simvastatin vs atorvastatin, we found an overall HR of 0.93 (95% CI 0.44-1.99) and 1.43 (95% CI 1.04-1.95), respectively. Broadening the outcome definition resulted in a HR of 1.13 (95% CI 0.58-2.22) for rosuvastatin and a HR of 1.29 (95% CI 1.01-1.66) for simvastatin. The number of events was low in cohorts IV and V (Appendix Table 12).

Table 1 Baseline covariates by treatment group in the primary prevention cohorts of pravastatin vs simvastatin and rosuvastatin vs atorvastatin after propensity score matching (simvastatin vs atorvastatin in Appendix Table 4)

	Low-intensity statin therapy			Moderate- to high-intensity statin therapy		
Covariate	**Pravastatin N = 9,703**	**Simvastatin N = 9,703**	**ASD (%)**	**Rosuvastatin N = 7,032**	**Atorvastatin N = 7,032**	**ASD (%)**
Age [years], mean (SD)	63.1 (9.8)	63.0 (9.8)	1.1	61.0 (9.9)	61.1 (9.9)	-1.0
Male, n (%)	4,887 (50.4)	4,960 (51.1)	-1.5	3,411 (48.5)	3,364 (47.8)	1.3
Current smoker*, n (%)	1,950 (20.1)	2,009 (20.7)	-1.5	1,376 (19.6)	1,321 (18.8)	2.0
>14 alcohol units/week*, n (%)	809 (8.3)	824 (8.5)	-0.6	709 (10.1)	698 (9.9)	0.5
Obesity*, n (%)	2,531 (26.1)	2,547 (26.2)	-0.4	2,104 (29.9)	2,109 (30.0)	-0.2
Comorbidities, n (%) - at any time before the cohort entry date, if not specified otherwise						
Hyperlipidemia	4,912 (50.6)	4,867 (50.2)	0.9	4,877 (69.4)	4,916 (69.9)	-1.2
Diabetes mellitus	2,097 (21.6)	2,165 (22.3)	-1.7	1,505 (21.4)	1,497 (21.3)	0.3
Hypertension	4,750 (49.0)	4,754 (49.0)	-0.1	3,614 (51.4)	3,663 (52.1)	-1.4
Heart failure	400 (4.1)	375 (3.9)	1.3	116 (1.6)	124 (1.8)	-0.9
Atrial fibrillation	790 (8.1)	716 (7.4)	2.9	216 (3.1)	219 (3.1)	-0.2
Ischemic heart disease	2,629 (27.1)	2,619 (27.0)	0.2	698 (9.9)	713 (10.1)	-0.7
Peripheral arterial disease	492 (5.1)	464 (4.8)	1.3	148 (2.1)	132 (1.9)	1.6
Hemorrhagic stroke	82 (0.8)	99 (1.0)	-1.8	30 (0.4)	29 (0.4)	0.2
Chronic kidney disease	575 (5.9)	535 (5.5)	1.8	482 (6.9)	487 (6.9)	-0.3
Severe liver impairment	27 (0.3)	34 (0.4)	-1.3	X	5 (0.1)	X
Hypothyroidism	658 (6.8)	641 (6.6)	0.7	521 (7.4)	505 (7.2)	0.9
Hyperthyroidism	161 (1.7)	160 (1.6)	0.1	104 (1.5)	103 (1.5)	0.1
Rheumatoid Arthritis	166 (1.7)	163 (1.7)	0.2	97 (1.4)	107 (1.5)	-1.2
Osteoarthritis	1,862 (19.2)	1,812 (18.7)	1.3	1,242 (17.7)	1,272 (18.1)	-1.1
Pre-existing muscle complaints	842 (8.7)	830 (8.6)	0.4	574 (8.2)	571 (8.1)	0.2
Musculoskeletal injuries	2,821 (29.1)	2,843 (29.3)	-0.5	2,139 (30.4)	2,139 (30.4)	0.0
COPD	439 (4.5)	446 (4.6)	-0.3	228 (3.2)	238 (3.4)	-0.8
Macular degeneration	84 (0.9)	82 (0.8)	0.2	37 (0.5)	41 (0.6)	-0.8
Falls†	265 (2.7)	256 (2.6)	0.6	175 (2.5)	189 (2.7)	-1.3
Pressure ulcer†	54 (0.6)	60 (0.6)	-0.8	26 (0.4)	19 (0.3)	1.8
Incontinence†	70 (0.7)	66 (0.7)	0.5	53 (0.8)	59 (0.8)	-1.0
Peripheral venous thrombosis†	155 (1.6)	169 (1.7)	-1.1	98 (1.4)	100 (1.4)	-0.2
Pneumonia†	66 (0.7)	71 (0.7)	-0.6	27 (0.4)	33 (0.5)	-1.3
Dysphagia†	65 (0.7)	56 (0.6)	1.2	30 (0.4)	34 (0.5)	-0.8
Anemia†	207 (2.1)	230 (2.4)	-1.6	94 (1.3)	91 (1.3)	0.4
Comedication, n (%) - in the 180 days before the cohort entry date						
Fibrates	131 (1.4)	138 (1.4)	-0.6	174 (2.5)	175 (2.5)	-0.1
Amiodarone	185 (1.9)	157 (1.6)	2.2	21 (0.3)	24 (0.3)	-0.8
Systemic corticosteroids	380 (3.9)	400 (4.1)	-1.0	215 (3.1)	223 (3.2)	-0.7
Antipsychotics	41 (0.4)	39 (0.4)	0.3	44 (0.6)	41 (0.6)	0.6
H_2-receptor antagonists	539 (5.6)	531 (5.5)	0.4	196 (2.8)	204 (2.9)	-0.7
Benzodiazepines	842 (8.7)	810 (8.3)	1.2	527 (7.5)	520 (7.4)	0.4
Number of cardiovascular drug classes						
0	1,760 (18.1)	1,788 (18.4)	-0.7	2,240 (31.9)	2,197 (31.2)	1.3

1 to 3	5,807 (59.8)	5,835 (60.1)	-0.6	4,063 (57.8)	4,059 (57.7)	0.1
4 to 10	2,136 (22.0)	2,080 (21.4)	1.4	729 (10.4)	776 (11.0)	-2.2
Number of general practitioner visits‡, mean (SD)	20.6 (13.4)	20.6 (13.1)	-0.1	19.0 (12.2)	19.0 (12.6)	0.3
Hospitalization†, n (%)	2,743 (28.3)	2,787 (28.7)	-1.0	1,727 (24.6)	1,717 (24.4)	0.3
Daily statin dose [mg], n (%)						
20 (P), 10 (S)	4,405 (45.4)	4,453 (45.9)	-1.0	NA	NA	
40 (P), 20 (S)	5,298 (54.6)	5,250 (54.1)	1.0	NA	NA	
40 (S), 5 (R), 10 (A)	NA	NA		695 (9.9)	714 (10.2)	-0.9
80 (S), 10 (R), 20 (A)	NA	NA		6,088 (86.6)	6,069 (86.3)	0.8
20 (R), 40 (A)	NA	NA		226 (3.2)	228 (3.2)	-0.2
40 (R), 80 (A)	NA	NA		23 (0.3)	21 (0.3)	0.5
Cohort entry date, n (%)						
2000-2001	2,912 (30.0)	2,912 (30.0)	0.0	NA	NA	
2002-2003	4,202 (43.3)	4,202 (43.3)	0.0	1,410 (20.1)	1,410 (20.1)	0.0
2004-2005	1,408 (14.5)	1,408 (14.5)	0.0	3,132 (44.5)	3,132 (44.5)	0.0
2006-2007	321 (3.3)	321 (3.3)	0.0	1,263 (18.0)	1,263 (18.0)	0.0
2008-2009	214 (2.2)	214 (2.2)	0.0	556 (7.9)	556 (7.9)	0.0
2010-2011	246 (2.5)	246 (2.5)	0.0	338 (4.8)	338 (4.8)	0.0
2012-2013	284 (2.9)	284 (2.9)	0.0	144 (2.0)	144 (2.0)	0.0
2014-2015	88 (0.9)	88 (0.9)	0.0	110 (1.6)	110 (1.6)	0.0
2016-2017	28 (0.3)	28 (0.3)	0.0	79 (1.1)	79 (1.1)	0.0

ASD absolute standardized difference; *SD* standard deviation; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality); *COPD* chronic obstructive pulmonary disease; *P* pravastatin; *S* simvastatin; *R* rosuvastatin; *A* atorvastatin; *NA* not applicable

* Last record before the cohort entry date.

† Assessed in the 3 years before the cohort entry date.

‡ Assessed in the 1 year before the cohort entry date.

Table 2 Censoring reasons and duration of follow-up for the primary prevention cohorts after propensity score matching

Low-intensity statin therapy		
	Pravastatin 20-40 mg N = 9,703	**Simvastatin 10-20 mg N = 9,703**
Censoring reasons, n (%)		
Muscular event (Outcome)	82 (0.8)	98 (1.0)
Recording of statin intolerance	17 (0.2)	47 (0.5)
Treatment switch	1,287 (13.3)	716 (7.4)
Discontinuation of statin treatment	1,758 (18.1)	1,802 (18.6)
Death	40 (0.4)	26 (0.3)
Recording of an exclusion criterion	198 (2.0)	175 (1.8)
Myocardial infarction or ischemic stroke	283 (2.9)	206 (2.1)
End of study enrollment	6,038 (62.2)	6,633 (68.4)
Duration of follow-up		
Mean number of days (standard deviation)	285.0 (112.5)	295.4 (109.1)
Median number of days (interquartile range)	365 (183-365)	365 (212-365)
Moderate- to high-intensity statin therapy		
	Rosuvastatin 5-40 mg N = 7,032	**Atorvastatin 10-80 mg N = 7,032**
Censoring reasons, n (%)		
Muscular event (Outcome)	100 (1.4)	86 (1.2)
Recording of statin intolerance	20 (0.3)	22 (0.3)
Treatment switch	678 (9.6)	661 (9.4)
Discontinuation of statin treatment	1,408 (20.0)	1,378 (19.6)
Death	8 (0.1)	15 (0.2)
Recording of an exclusion criterion	126 (1.8)	135 (1.9)
Myocardial infarction or ischemic stroke	59 (0.8)	81 (1.2)
End of study enrollment	4,633 (65.9)	4,654 (66.2)
Duration of follow-up		
Mean number of days (standard deviation)	292.1 (110.5)	293.7 (108.3)
Median number of days (interquartile range)	365 (205-365)	365 (208-365)
	Simvastatin 40-80 mg N = 37,743	**Atorvastatin 10-20 mg N = 37,743**
Censoring reasons, n (%)		
Muscular event (Outcome)	483 (1.3)	368 (1.0)
Recording of statin intolerance	214 (0.6)	166 (0.4)
Treatment switch	3,529 (9.4)	3,156 (8.4)
Discontinuation of statin treatment	7,279 (19.3)	7,526 (19.9)
Death	110 (0.3)	91 (0.2)
Recording of an exclusion criterion	686 (1.8)	651 (1.7)
Myocardial infarction or ischemic stroke	713 (1.9)	467 (1.2)
End of study enrollment	24,729 (65.5)	25,318 (67.1)
Duration of follow-up		
Mean number of days (standard deviation)	282.6 (115.4)	287.3 (110.8)
Median number of days (interquartile range)	365 (176-365)	365 (188-365)

Table 3 Incidence rates of the muscular events in the primary prevention cohorts before and after propensity score matching

	Number (%) of muscular events		Total person-years of follow-up		Incidence rate per 1,000 person-years	
	Exposed	**Comparator**	**Exposed**	**Comparator**	**Exposed**	**Comparator**
Low-intensity statin therapy						
Pravastatin vs Simvastatin (ref)						
Crude	82 (0.8)	2,205 (1.2)	7,584	143,220	10.8	15.4
PS-matched	82 (0.8)	98 (1.0)	7,577	7,852	10.8	12.5
Moderate- to high-intensity statin therapy						
Rosuvastatin vs Atorvastatin (ref)						
Crude	101 (1.4)	854 (1.0)	5,648	64,369	17.9	13.3
PS-matched	100 (1.4)	86 (1.2)	5,628	5,658	17.8	15.2
Simvastatin vs Atorvastatin (ref)						
Crude	2,456 (1.5)	957 (0.9)	124,546	78,697	19.7	12.2
PS-matched	483 (1.3)	368 (1.0)	29,222	29,708	16.5	12.4

Ref reference; *PS* propensity score

Table 4 Hazard ratios for muscular events in the primary prevention cohorts before and after propensity score matching

	Hazard ratio (95% CI)	
	Crude	**PS-matched**
Low-intensity statin therapy		
Pravastatin vs Simvastatin (ref)		
Overall	0.70 (0.56-0.87)	0.86 (0.64-1.16)
Time-specific* [days of follow-up]		
1-30	0.41 (0.21-0.80)	0.60 (0.26-1.37)
31-90	0.51 (0.31-0.83)	0.60 (0.32-1.11)
91-180	0.74 (0.48-1.13)	0.97 (0.54-1.74)
181-365	1.02 (0.73-1.44)	1.13 (0.70-1.82)
Moderate- to high-intensity statin therapy		
Rosuvastatin vs Atorvastatin (ref)		
Overall	1.36 (1.11-1.68)	1.17 (0.88-1.56)
Time-specific* [days of follow-up]		
1-30	1.44 (0.84-2.46)	1.15 (0.55-2.42)
31-90	1.56 (1.07-2.28)	1.43 (0.82-2.50)
91-180	1.17 (0.75-1.81)	1.24 (0.66-2.31)
181-365	1.33 (0.93-1.90)	0.97 (0.60-1.57)
Simvastatin vs Atorvastatin (ref)		
Overall	1.62 (1.50-1.75)	1.33 (1.16-1.53)
Time-specific* [days of follow-up]		
1-30	1.86 (1.55-2.24)	1.91 (1.29-2.81)
31-90	1.65 (1.43-1.91)	1.46 (1.13-1.88)
91-180	1.57 (1.36-1.82)	1.31 (1.00-1.71)
181-365	1.51 (1.32-1.73)	1.09 (0.86-1.38)

CI confidence interval; *PS* propensity score; *Ref* reference

* Patients whose follow-up ended before the time window of interest were excluded from the respective analysis. We censored patients on the day of the end of the time window of interest in any given analysis.

Table 5 Hazard ratios for subgroup, sensitivity, and additional analyses for muscular events in the primary prevention cohorts after propensity score matching

	Number of events		Total person-years of follow-up		HR (95% CI)
	Exposed	Comparator	Exposed	Comparator	
Low-intensity statin therapy					
Pravastatin vs Simvastatin (ref)					
Subgroup analyses					
Male	33	46	3,860	3,938	0.73 (0.47-1.14)
Female	49	51	3,711	3,860	0.99 (0.67-1.47)
40-64 years	39	58	3,903	4,028	0.69 (0.46-1.04)
≥65 years	43	54	3,665	3,743	0.81 (0.54-1.21)
20 vs 10 mg	35	49	3,458	3,562	0.73 (0.47-1.13)
40 vs 20 mg	47	59	4,110	4,258	0.82 (0.56-1.21)
Sensitivity analyses					
No muscle complaints before CED	71	98	6,932	7,120	0.74 (0.55-1.01)
No use of CYP3A4 inhibiting drugs*	57	69	5,272	5,463	0.85 (0.60-1.21)
Additional analyses					
Censoring if dosage change	75	88	7,034	6,966	0.85 (0.62-1.15)
Broader outcome definition†	99	145	7,577	7,852	0.70 (0.54-0.91)
Moderate- to high-intensity statin therapy					
Rosuvastatin vs Atorvastatin (ref)					
Subgroup analyses					
Male	42	36	2,744	2,773	1.18 (0.76-1.84)
Female	57	43	2,862	2,905	1.34 (0.90-1.99)
40-64 years	59	44	3,448	3,478	1.35 (0.92-2.00)
≥65 years	42	23	2,122	2,141	1.84 (1.11-3.06)
5-10 vs 10-20 mg	95	70	5,426	5,490	1.37 (1.01-1.87)
20-40 vs 40-80 mg	X	5	188	184	0.59 (0.14-2.47)
Sensitivity analyses					
No muscle complaints before CED	88	74	5,179	5,238	1.20 (0.88-1.64)
No use of CYP3A4 inhibiting drugs*	79	63	4,460	4,475	1.26 (0.90-1.75)
Additional analyses					
Censoring if dosage change	96	84	5,395	5,196	1.11 (0.83-1.48)
Broader outcome definition†	120	108	5,628	5,658	1.12 (0.86-1.45)
Simvastatin vs Atorvastatin (ref)					
Subgroup analyses					
Male	215	152	14,952	15,144	1.43 (1.16-1.76)
Female	279	204	14,204	14,494	1.39 (1.16-1.67)
40-64 years	251	198	16,280	16,638	1.29 (1.07-1.56)
≥65 years	238	159	12,753	12,910	1.52 (1.24-1.85)
40 vs 10 mg	502	352	28,972	29,517	1.45 (1.27-1.66)
80 vs 20 mg	X	X	191	197	1.01 (0.20-5.01)
Sensitivity analyses					
No muscle complaints before CED	413	287	26,347	26,782	1.46 (1.26-1.70)
No use of CYP3A4 inhibiting drugs*	349	290	21,661	21,932	1.22 (1.04-1.42)

Additional analyses					
Censoring if dosage change	468	335	27,920	27,451	1.38 (1.20-1.59)
Broader outcome definition†	697	534	29,222	29,708	1.33 (1.18-1.48)

HR hazard ratio; *CI* confidence interval; *Ref* reference; *CED* cohort entry date; *CYP3A4* Cytochrome P450 3A4; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

* The analysis was restricted to patients with no prescription for azole antifungals, macrolide antibiotics, cimetidine, cyclosporine, nefazodone, amiodarone, amlodipine, diltiazem, and verapamil within 180 days before the cohort entry date. We censored patients on the day of a first prescription for one of the drugs during follow-up.

† Any recorded Read code for 'statin intolerance' qualified as an outcome of interest.

Discussion

Findings of this large primary care database cohort study do not suggest a systematically reduced risk of muscular events for hydrophilic statins when compared to lipophilic statins at comparable lipid-lowering doses. In the primary prevention study population, results pointed towards a lower muscular risk for pravastatin (hydrophilic) than simvastatin (lipophilic) at doses used for the low-intensity statin therapy, and towards a lower risk of muscular events for atorvastatin (lipophilic) than rosuvastatin (hydrophilic) and simvastatin (lipophilic), when compared at doses used for the moderate- to high-intensity statin therapy. Our results did not reach statistical significance for all comparisons. However, point estimates were furthest from the null within the first 90 days after statin initiation, which provides confidence in the validity of our findings, as statin-associated muscular adverse events predominately occur within the first 6 months after treatment start.[31]

Findings from RCTs comparing statins head-to-head have suggested a comparable tolerability for hydrophilic and lipophilic statins at comparable lipid-lowering doses.[11,12,32] However, the limited sample size of the trials resulted in a low absolute number of muscular events. More importantly, head-to-head RCTs were designed to evaluate statins' efficacy in the reduction of low-density lipoprotein cholesterol and were not restricted to new statin users. Given that muscular adverse events typically manifest shortly after statin initiation,[31] inclusion of tolerant prevalent statin users may have resulted in depletion of susceptibles and may have biased safety results towards the null. For instance, the POLARIS trial, a double-blind RCT with a 26-week follow-up, included 871 patients with hypercholesterolemia with or without cardiovascular disease and randomized them to rosuvastatin 40 mg or atorvastatin 80 mg after a dietary run-in period. The study reported 3.0% (n=13/432) of drug-related myalgia for rosuvastatin and 3.6% (n=16/439) for atorvastatin. However, data on the patient characteristics at study entry are limited and do not provide details on prior statin use.[11] The same is true for the open-label randomized Dutch DISCOVERY trial, which included hypercholesterolemic patients with or without atherosclerotic disease from 152 primary care physician practices. The authors found that pravastatin 40 mg and simvastatin 20 mg were similarly well tolerated, with 2.4% (n= 5/211) of pravastatin users and 1.5% (n= 3/194) of simvastatin users having adverse events of myalgia over 12 weeks of follow-up. Although the study reported that around 20% of patients in either treatment group had taken statins in the 4 weeks before enrolment, data on the ever statin use of patients before this date are not available.[12]

The former hypothesis of a systematically reduced muscular risk in association with hydrophilic statins was based on *in-vitro* data demonstrating a lower cytotoxicity on C2C12 myotubes for

hydrophilic statins than lipophilic statins,[10] and in particular on the consideration that hydrophilic statins penetrate skeletal muscles less easily due to lower passive diffusion.[8] However, the risk of muscular adverse events of statins may depend on different pharmacokinetic processes. For instance, statins are substrates of the organic anion transporting polypeptide (OATP) transport proteins, which are involved in the hepatic and muscular uptake of statins.[33] It has been discussed that different statins may bind to these transporters with different affinities,[33,34] which could eventually lead to different intramuscular drug concentrations and thus to different risk profiles for muscular adverse events. In addition, polymorphisms in the SLCO1B1 gene, which encodes the OATP1B1 hepatic uptake transporter, have been linked to reduced transport activity and increased plasma statin levels.[34,35] Levels of simvastatin were found to be particularly affected by these genetic polymorphisms,[34] which may explain the elevated muscular risk for simvastatin observed in the current study. Differences in the metabolism of statins, i.e. their susceptibility for CYP3A4-mediated interactions do probably not explain current findings since results from the sensitivity analysis restricted to patients without use of CYP3A4 inhibiting drugs were comparable to those from the primary analysis.

In this study, we observed an absolute risk of muscular events of 1.3% in all new statin users (1.9% when we included all recordings of statin intolerance). Other observational studies reported higher risks for patients in the routine care setting; the PRIMO study, a countrywide survey including 7,924 patients with hyperlipidemia and high-dosage statin therapy in France, reported an absolute risk of muscular events of 10.5%.[36] A cohort study performed in 120 Swedish statin initiators and with a follow-up of one year reported an absolute risk of 14%.[37] Differences in findings may be explained by the varying data sources and outcome definitions. We defined muscular events based on Read codes recorded in electronic primary care records, whereas the PRIMO study conducted standardized interviews, and the Swedish cohort study used patient questionnaires to specifically enquire about muscular symptoms.[36,37] While the latter approaches may have overestimated the absolute risk of muscular adverse events, we likely underestimated the absolute risk of muscular events, as general practitioners may have modified statin treatment without specifically recording the presumptive adverse event. However, any such outcome misclassification was most likely non-differential and thus, if at all, biased HRs towards unity.[38]

In the comparison of low-intensity statin therapy with pravastatin vs simvastatin, more pravastatin users (13.3%) than simvastatin users (7.4%) were censored due to treatment switch. The imbalance of censoring reasons may be related to the intensified target levels for low-density lipoprotein cholesterol published in the European guidelines in 2003[39] or the British

guidelines in 2005.[40] Lower therapeutic targets have probably caused general practitioners to intensify statin treatment in patients taking low-intensity statin therapy by either treatment switch or dosage increase, if higher doses were available (8.2% of pravastatin vs 14.9% of simvastatin users were censored due to dosage increase in the additional censoring analysis). When we restricted the comparison of pravastatin vs simvastatin to statin users with a CED between 2000 and 2001, i.e. with end of follow-up before 2003, the comparative muscular risk remained unchanged, but censoring reasons including treatment switch were almost balanced ($\Delta<2\%$) between treatment groups.

Some additional limitations need to be considered. First, small sample size in the secondary prevention cohorts prevented calculation of reliable risk estimates. We therefore focused on the study results from the primary prevention cohorts, though we did present all findings for completeness. Second, the dose ratios at which statin doses are comparable in efficacy may vary depending on the literature source. Third, rosuvastatin was the only study drug that was newly licensed in the United Kingdom after 1997, i.e. in March 2003.[16] If bias due to new drug recording in the rosuvastatin group had been present, we would have overestimated the HR of rosuvastatin vs atorvastatin. However, when we restricted the analysis of rosuvastatin vs atorvastatin to users with a CED 2 years after licensing of the former, the HR of muscular events did not change. Fourth, because 98% of our observed events were related to myalgia and not to myositis or rhabdomyolysis, reported HRs primarily refer to the risk of mild statin-associated muscle symptoms. Finally, after PS matching, baseline characteristics were balanced between treatment groups compared, but not necessarily between cohorts. Thus, indirect comparison of the muscular risk of rosuvastatin vs simvastatin, both used for the moderate- to high-intensity statin therapy, was not possible.

In conclusion, this study of United Kingdom-based primary health care data does not suggest a systematically reduced risk of muscular events for hydrophilic statins when compared with lipophilic statins at comparable lipid-lowering doses. Low-intensity statin therapy with hydrophilic pravastatin (vs lipophilic simvastatin) and moderate- to high-intensity statin therapy with lipophilic atorvastatin (vs hydrophilic rosuvastatin and lipophilic simvastatin) may be associated with a decreased muscular risk. However, further studies that replicate our findings are warranted before implications for clinical practice can be concluded.

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Conflicts of Interest

Alexandra M Mueller, Evangelia Liakoni, and Stephan Krähenbühl report grants from Sanofi, during the conduct of the study. Cornelia Schneider, Theresa Burkard, Susan S Jick, Christoph R Meier, and Julia Spoendlin declare to have no conflicts of interest.

Data availability

Due to official regulations by the data provider, sharing of analytical datasets is strictly prohibited. Any analytical data has to be stored on a pre-specified and agreed upon server with strict access control. Data can be requested via an official data request submitted to the CPRD.

Additional statement

This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

References

1. National Institute for Health and Care Excellence. Clinical guideline CG181 - Cardiovascular disease: risk assessment and reduction, including lipid modification. https://www.nice.org.uk/guidance/cg181. Published 2014. Accessed November 25, 2019.
2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111-188.
3. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy - European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36:1012-1022.
4. Joy TR, Hegele RA. Narrative review: statin-related myopathy. Ann Intern Med. 2009;150:858-868.
5. Mammen AL, Amato AA. Statin myopathy: A review of recent progress. Curr Opin Rheumatol. 2010;22:644-650.
6. Auer J, Sinzinger H, Franklin B, Berent R. Muscle- and skeletal-related side-effects of statins: tip of the iceberg?. Eur J Prev Cardiol. 2016;23:88-110.
7. Chatzizisis YS, Koskinas KC, Misirli G, Vaklavas C, Hatzitolios A, Giannoglou GD. Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment, prevention and treatment. Drug Saf. 2010;33:171-187.
8. Bitzur R, Cohen H, Kamari Y, Harats D. Intolerance to statins: Mechanisms and management. Diabetes Care. 2013;36 Suppl 2:S325-S330.
9. Turner RM, Pirmohamed M. Statin-Related Myotoxicity: A Comprehensive Review of Pharmacokinetic, Pharmacogenomic and Muscle Components. J Clin Med. 2019;9:22.
10. Bonifacio A, Sanvee GM, Bouitbir J, Krähenbühl S. The AKT/mTOR signaling pathway plays a key role in statin-induced myotoxicity. Biochim Biophys Acta. 2015;1853:1841-1849.
11. Leiter LA, Rosenson RS, Stein E, et al. Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: Results of the POLARIS study. Atherosclerosis. 2007;194:e154-e164.
12. Bots AF, Kastelein JJ. Discovery Netherlands Investigators. Achieving lipid goals in real life: The Dutch DISCOVERY study. Int J Clin Pract. 2005;59:1387-1394.
13. Ghosh RE, Crellin E, Beatty S, Donegan K, Myles P, Williams R. How Clinical Practice Research Datalink data are used to support pharmacovigilance. Ther Adv Drug Saf. 2019;10:2042098619854010.
14. Strom BL, Kimmel SE, Hennessy S. Electronic Health Record Databases. In: Pharmacoepidemiology. Sixth edit. Hoboken, NJ: Wiley-Blackwell; 2020:241-289.
15. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44:827-836.
16. Electronic medicines compendium. Crestor 10 mg film-coated tablets - Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/7559/smpc. Accessed February 11, 2020.
17. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: Prospective open cohort study using a primary care database. BMJ. 2016;353:i3305.
18. Mancini GB, Baker S, Bergeron J, et al. Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016). Can J Cardiol. 2016;32:S35-S65.
19. Dalakas MC. Toxic and drug-induced myopathies. J Neurol Neurosurg Psychiatry. 2009;80:832-838.

20. Laufs U, Scharnagl H, Halle M, Windler E, Endres M, März W. Treatment Options for Statin-Associated Muscle Symptoms. Dtsch Arztebl Int. 2015;112:748-755.
21. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016;45:353-360.
22. Patorno E, Grotta A, Bellocco R, Schneeweiss S. Propensity score methodology for confounding control in health care utilization databases. Epidemiol Biostat Public Health. 2013;10:e8940.
23. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399-424.
24. Department of Health and Social Care. National Service Framework for Coronary Heart Disease. Modern Standards and Service Models. London: Department of Health and Social Care; 2000. https://www.gov.uk/government/publications/quality-standards-for-coronary-heart-disease-care.
25. Cooper A, O'Flynn N. Guideline Development Group. Risk assessment and lipid modification for primary and secondary prevention of cardiovascular disease: Summary of NICE guidance. BMJ. 2008;336:1246-1248.
26. Helin-Salmivaara A, Lavikainen P, Aarnio E, Huupponen R, Korhonen MJ. Sequential cohort design applying propensity score matching to analyze the comparative effectiveness of atorvastatin and simvastatin in preventing cardiovascular events. PLoS One. 2014;9:e90325.
27. Rubin DB. Using propensity scores to help design observational studies: Application to the tobacco litigation. Health Services & Outcomes Research Methodology. 2001;2:169-188.
28. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput. 2009;38:1228-1234.
29. Sathasivam S. Statin induced myotoxicity. Eur J Intern Med. 2012;23:317-324.
30. Rowan CG, Brunelli SM, Munson J, et al. Clinical importance of the drug interaction between statins and CYP3A4 inhibitors: a retrospective cohort study in The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2012;21:494-506.
31. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - An attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci. 2015;11:1-23.
32. Wlodarczyk J, Sullivan D, Smith M. Comparison of benefits and risks of rosuvastatin versus atorvastatin from a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol. 2008;102:1654-1662.
33. Bouitbir J, Sanvee GM, Panajatovic MV, Singh F, Krähenbühl S. Mechanisms of statin-associated skeletal muscle-associated symptoms. Pharmacol Res. 2020;154:104201.
34. Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010;87:130-133.
35. Moßhammer D, Schaeffeler E, Schwab M, Mörike K. Mechanisms and assessment of statin-related muscular adverse effects. Br J Clin Pharmacol. 2014;78:454-466.
36. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients - The PRIMO study. Cardiovasc Drugs Ther. 2005;19:403-414.
37. Skilving I, Eriksson M, Rane A, Ovesjö ML. Statin-induced myopathy in a usual care setting—a prospective observational study of gender differences. Eur J Clin Pharmacol. 2016;72:1171-1176.
38. Funk MJ, Landi SN. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. Curr Epidemiol Rep. 2014;1:175-185.
39. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and

Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003;24:1601-1610.
40. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005;91 Suppl 5:v1-v52.

Supplemental materials

Appendix Table 1. List of Read codes for the outcome of a muscular event

I.	
1DCC.00	Aching muscles
N241012	Muscle pain
N241000	Myalgia unspecified
R01z200	Musculoskeletal pain
N241z00	Myalgia or myositis NOS
N241.00	Myalgia and myositis unspecified
N241100	Myositis unspecified
Nyu8000	Other myositis
F39W.00	Inflammatory myopathy; not elsewhere classified
N233300	Rhabdomyolysis
K045.00	Acute renal failure due to non-traumatic rhabdomyolysis
SK08.00	Acute renal failure due to rhabdomyolysis
R113.00	Myoglobinuria
F394000	Drug-induced myopathy
F394.00	Toxic myopathy
F397.00	Proximal myopathy
Fyu8200	Other specified myopathies
Nyu8.00	Disorders of muscles*
Nyu8500	Other specified disorders of muscle*
Nyu8B00	Disorder of muscle; unspecified*
N233.00	Other specific muscle disorder*
N233z00	Other specific muscle disorder*
II.†	
8I76.00	Statin not tolerated
U60CA00	Statin causing adverse effect in therapeutic use
TJC2400	Adverse reaction to simvastatin
U60C615	Adverse reaction to simvastatin
TJC2500	Adverse reaction to pravastatin
U60C616	Adverse reaction to pravastatin

* These 5 Read codes resulted in one outcome event in total.
† If followed by a Read code listed under I. within 90 days.

Appendix Table 2. Set of baseline covariates

Demographics	**Comedication**
Age	*recorded in the 180 days before the cohort entry date*
Sex	Fibrates
Lifestyle factors	Drugs causing myopathy
last record entry before the cohort entry date	Amiodarone
Smoking status	Systemic corticosteroids
current vs former or never	Antipsychotics (i.e. clozapine, risperidone, olanzapine, loxapine, haloperidol)
Alcohol consumption	Indicators for health status / frailty
≤ vs >14 units of alcohol per week	H_2-receptor antagonists
Comorbidities	Benzodiazepine
recorded at any time before the cohort entry date	Number of cardiovascular drug classes
Diabetes mellitus†	0, 1-3, or 4-10 drug classes, including
Chronic kidney disease‡	ACE inhibitors
Severe liver impairment	Angiotensin II receptor blockers
Hypo-/ Hyperthyroidism	Beta blockers
Pre-existing muscle complaints	Calcium channel blockers
Musculoskeletal injuries	Coronary vasodilators
Indicators for health status / frailty	Diuretics
Myocardial infarction§	Antiarrhythmics
Ischemic stroke§	Antiplatelet agents
Hemorrhagic stroke	Vitamin K antagonists
Hypertension	Other lipid-lowering agents (ezetimibe, fibrates, nicotinic acid and derivatives, bile acid sequestrants, omega-3 fatty acid compounds)
Heart failure	**Health care utilization**
Atrial fibrillation	*in the year before the cohort entry date*
Ischemic heart disease	Number of general practitioner visits
Peripheral arterial disease	*recorded in the 3 years before the cohort entry date*
Hyperlipidemia‖	Hospitalization
Rheumatoid Arthritis	**Other variables**
Osteoarthritis	*last record entry before the cohort entry date*
Chronic obstructive pulmonary disease	Obesity
Macular degeneration	body mass index < 30 vs ≥ 30 kg/m^2
recorded in the 3 years before the cohort entry date	*at the date of cohort entry*
Falls	Initially prescribed daily statin dose
Pressure ulcer	
Incontinence	
Peripheral venous thrombosis	
Pneumonia	
Dysphagia	
Anemia	

ACE angiotensin-converting enzyme

* The following covariates were not included in the statistical analyses due to a prevalence of <0.5% among eligible statin initiators, irrespective of statin type: comorbidities: hypo-/hyperparathyroidism, vitamin D deficiency, Cushing's syndrome, adrenal insufficiency, lupus erythematosus, scleroderma, Sjoegren's syndrome, mixed connective disease, sarcoidosis, polyarteritis nodosa, and Down syndrome; comedication: niacin, D-penicillamine, colchicine, hydroxy-/chloroquine, interferons, and fusidic acid.

† Defined as either a Read code for diabetes mellitus or a recorded prescription for an antidiabetic drug ≤180 days before the cohort entry date.

‡ Defined as either a Read code for chronic kidney disease or two successive glomerular filtration rate measurements <60 ml/min, separated by ≥90 days, with the first measurement being the closest before the cohort entry date.

§ Only assessed in the secondary prevention cohorts.

‖ Defined as either a Read code for hyperlipidemia or a last recorded low-density lipoprotein level of ≥3 mmol/L before the cohort entry date.

Appendix Table 3. Detailed information on the subgroup analyses, sensitivity analyses, and additional analyses

Subgroup analyses	We performed subgroup analyses by • sex, • age, i.e. </≥ 65 years, • initial daily statin dose, i.e. ≤/> 20 mg of pravastatin; ≤/> 10 mg of rosuvastatin; ≤/> 40 mg of simvastatin; equivalent doses of the comparator statins: ≤/> 10 mg of simvastatin; ≤/> 20 mg of atorvastatin; ≤/> 10 mg of atorvastatin. (primary prevention cohorts)
Sensitivity analysis 1: **No muscle complaints before the cohort entry date**	We performed a sensitivity analysis restricted to patients with no recording of muscle complaints (including myalgia, muscle pain, muscle ache, spasm, or cramps) at any time before the cohort entry date. (primary prevention cohorts)
Sensitivity analysis 2: **No use of CYP3A4 inhibiting drugs**	We performed a sensitivity analysis restricted to patients with no prescription for a drug that inhibits the enzyme CYP3A4 (i.e. azole antifungals, macrolide antibiotics, cimetidine, cyclosporine, nefazodone, amiodarone, amlodipine, diltiazem, and verapamil), within 6 months before the cohort entry date (censoring on the date of a first prescription during follow-up). Simvastatin and atorvastatin are metabolized by CYP3A4, and their serum concentrations may be increased if co-prescribed with CYP3A4 inhibiting drugs. (primary prevention cohorts)
Additional analysis 1: **Censoring if dosage change**	We additionally censored patients on the date of dosage change (prescription for a dose of the study drug other than the initially prescribed one). If a Read code for a muscular event was recorded within 90 days after dosage reduction, we considered the date of dosage reduction as the date when an event occurred. (primary prevention cohorts)
Additional analysis 2: **Broader outcome definition**	We performed an analysis applying a broader outcome definition, in which any recorded Read code for 'statin intolerance' qualified as an outcome of interest. (primary and secondary prevention cohorts)
Additional analysis 3: **Multivariable logistic regression analyses**	We repeated our analyses in the cohorts before propensity score matching, using multivariable logistic regression and adjusting for all baseline covariates as well as for calendar year of cohort entry. (primary and secondary prevention cohorts)

CYP3A4 Cytochrome P450 3A4

Appendix Table 4. Baseline covariates of users of simvastatin 40-80 mg and atorvastatin 10-20 mg (moderate- to high-intensity statin therapy) in the primary prevention cohort before and after propensity score matching

	Cohort before propensity score matching			Cohort after propensity score matching		
Covariate	**Simvastatin N = 161,572**	**Atorvastatin N = 101,359**	**Absolute standardized difference (%)**	**Simvastatin N = 37,743**	**Atorvastatin N = 37,743**	**Absolute standardized difference (%)**
Age [years], mean (SD)	61.0 (9.7)	61.8 (9.8)	-8.4	62.0 (9.8)	62.0 (9.9)	-0.4
Male, n (%)	88,473 (54.8)	49,358 (48.7)	12.2	19,176 (50.8)	19,152 (50.7)	0.1
Current smoker*, n (%)	36,067 (22.3)	18,994 (18.7)	8.9	7,314 (19.4)	7,222 (19.1)	0.6
>14 units of alcohol per week*, n (%)	19,569 (12.1)	9,995 (9.9)	7.2	3,719 (9.9)	3,784 (10.0)	-0.6
Obesity*, n (%)	55,138 (34.1)	32,248 (31.8)	4.9	12,349 (32.7)	12,341 (32.7)	0.0
Comorbidities, n (%) - at any time before the cohort entry date, if not specified otherwise						
Hyperlipidemia	113,122 (70.0)	68,675 (67.8)	4.9	24,565 (65.1)	24,664 (65.3)	-0.6
Diabetes mellitus	32,691 (20.2)	25,456 (25.1)	-11.7	9,892 (26.2)	9,896 (26.2)	-0.0
Hypertension	74,186 (45.9)	50,638 (50.0)	-8.1	19,159 (50.8)	19,168 (50.8)	-0.0
Heart failure	2,087 (1.3)	1,807 (1.8)	-4.0	734 (1.9)	768 (2.0)	-0.6
Atrial fibrillation	5,302 (3.3)	3,945 (3.9)	-3.3	1,539 (4.1)	1,553 (4.1)	-0.2
Ischemic heart disease	13,720 (8.5)	12,222 (12.1)	-11.8	4,734 (12.5)	4,777 (12.7)	-0.3
Peripheral arterial disease	3,628 (2.2)	2,779 (2.7)	-3.2	1,016 (2.7)	1,019 (2.7)	-0.0
Hemorrhagic stroke	1,098 (0.7)	562 (0.6)	1.6	283 (0.7)	273 (0.7)	0.3
Chronic kidney disease	12,667 (7.8)	7,202 (7.1)	2.8	2,941 (7.8)	3,035 (8.0)	-0.9
Severe liver impairment	196 (0.1)	135 (0.1)	-0.3	59 (0.2)	65 (0.2)	-0.4
Hypothyroidism	11,460 (7.1)	7,550 (7.4)	-1.4	2,948 (7.8)	2,886 (7.6)	0.6
Hyperthyroidism	2,620 (1.6)	1,721 (1.7)	-0.6	695 (1.8)	682 (1.8)	0.3
Rheumatoid Arthritis	2,622 (1.6)	1,658 (1.6)	-0.1	742 (2.0)	754 (2.0)	-0.2
Osteoarthritis	31,489 (19.5)	19,344 (19.1)	1.0	7,490 (19.8)	7,455 (19.8)	0.2
Pre-existing muscle complaints	16,071 (9.9)	9,620 (9.5)	1.5	3,772 (10.0)	3,716 (9.8)	0.5
Musculoskeletal injuries	57,913 (35.8)	33,078 (32.6)	6.8	12,734 (33.7)	12,651 (33.5)	0.5
Chronic obstructive pulmonary disease	7,205 (4.5)	3,926 (3.9)	2.9	1,585 (4.2)	1,571 (4.2)	0.2
Macular degeneration	1076 (0.7)	686 (0.7)	-0.1	278 (0.7)	293 (0.8)	-0.5
Falls†	4,673 (2.9)	2,780 (2.7)	0.9	1,201 (3.2)	1,149 (3.0)	0.8
Pressure ulcer†	552 (0.3)	387 (0.4)	-0.7	154 (0.4)	160 (0.4)	-0.2
Incontinence†	1,541 (1.0)	959 (0.9)	0.1	373 (1.0)	396 (1.0)	-0.6
Peripheral venous thrombosis†	1,905 (1.2)	1,299 (1.3)	-0.9	517 (1.4)	497 (1.3)	0.5
Pneumonia†	938 (0.6)	542 (0.5)	0.6	213 (0.6)	233 (0.6)	-0.7
Dysphagia†	1,026 (0.6)	544 (0.5)	1.3	233 (0.6)	230 (0.6)	0.1
Anemia†	2,976 (1.8)	1,840 (1.8)	0.2	773 (2.0)	763 (2.0)	0.2

Comedication, n (%) - in the 180 days before the cohort entry date						
Fibrates	697 (0.4)	1,433 (1.4)	-10.3	347 (0.9)	357 (0.9)	-0.3
Amiodarone	513 (0.3)	559 (0.6)	-3.6	231 (0.6)	221 (0.6)	0.3
Systemic corticosteroids	5,773 (3.6)	3,774 (3.7)	-0.8	1,441 (3.8)	1,438 (3.8)	0.0
Antipsychotics	1,219 (0.8)	555 (0.5)	2.6	207 (0.5)	197 (0.5)	0.4
H_2-receptor antagonists	3,870 (2.4)	3,605 (3.6)	-6.8	1,288 (3.4)	1,258 (3.3)	0.4
Benzodiazepines	9,529 (5.9)	7,019 (6.9)	-4.2	2,658 (7.0)	2,596 (6.9)	0.6
Number of cardiovascular drug classes						
0	52,285 (32.4)	30,680 (30.3)	4.5	10,108 (26.8)	10,112 (26.8)	-0.0
1 to 3	93,774 (58.0)	59,730 (58.9)	-1.8	22,878 (60.6)	22,836 (60.5)	0.2
4 to 10	15,513 (9.6)	10,949 (10.8)	-4.0	4,757 (12.6)	4,795 (12.7)	-0.3
Number of general practitioner visits‡, mean (SD)	19.8 (13.0)	20.2 (12.9)	-3.7	21.0 (13.2)	20.9 (13.2)	0.4
Hospitalization†, n (%)	54,000 (33.4)	30,092 (29.7)	8.0	11,719 (31.1)	11,623 (30.8)	0.6
Daily statin dose [mg], n (%)						
40 (simvastatin) vs 10 (atorvastatin)	161,318 (99.8)	65,325 (64.4)	104.2	37,490 (99.3)	37,490 (99.3)	0.0
80 (simvastatin) vs 20 (atorvastatin)	254 (0.2)	36,034 (35.6)	-104.2	253 (0.7)	253 (0.7)	0.0
Cohort entry date, n (%)						
2000-2001	417 (0.3)	13,531 (13.3)	-53.8	416 (1.1)	416 (1.1)	0.0
2002-2003	7,045 (4.4)	23,137 (22.8)	-56.0	7,045 (18.7)	7,045 (18.7)	0.0
2004-2005	16,211 (10.0)	24,286 (24.0)	-37.7	14,903 (39.5)	14,903 (39.5)	0.0
2006-2007	31,460 (19.5)	5,770 (5.7)	42.5	3,744 (9.9)	3,744 (9.9)	0.0
2008-2009	40,161 (24.9)	1,414 (1.4)	74.1	845 (2.2)	845 (2.2)	0.0
2010-2011	32,818 (20.3)	842 (0.8)	66.8	479 (1.3)	479 (1.3)	0.0
2012-2013	23,541 (14.6)	6,381 (6.3)	27.3	3,793 (10.0)	3,793 (10.0)	0.0
2014-2015	7,901 (4.9)	13,652 (13.5)	-30.0	4,755 (12.6)	4,755 (12.6)	0.0
2016-2017	2,018 (1.2)	12,346 (12.2)	-44.8	1,763 (4.7)	1,763 (4.7)	0.0

SD standard deviation

* Last record before the cohort entry date.

† Assessed in the 3 years before the cohort entry date.

‡ Assessed in the 1 year before the cohort entry date.

Appendix Table 5. Baseline covariates of users of pravastatin 20-40 mg and simvastatin 10-20 mg (low-intensity statin therapy) in the secondary prevention cohort before and after propensity score matching

	Cohort before propensity score matching			Cohort after propensity score matching		
Covariate	**Pravastatin N = 4,139**	**Simvastatin N = 24,836**	**Absolute standardized difference (%)**	**Pravastatin N = 4,121**	**Simvastatin N = 4,121**	**Absolute standardized difference (%)**
Age [years], mean (SD)	65.9 (9.7)	67.3 (9.2)	-14.7	65.9 (9.7)	65.9 (9.7)	0.3
Male, n (%)	2,582 (62.4)	14,717 (59.3)	6.4	2,574 (62.5)	2,619 (63.6)	-2.3
Current smoker*, n (%)	1,050 (25.4)	5,478 (22.1)	7.8	1,048 (25.4)	1,017 (24.7)	1.7
>14 units of alcohol per week*, n (%)	335 (8.1)	2,128 (8.6)	-1.7	334 (8.1)	313 (7.6)	1.9
Obesity*, n (%)	835 (20.2)	5,049 (20.3)	-0.4	830 (20.1)	847 (20.6)	-1.0
Comorbidities, n (%) - at any time before the cohort entry date, if not specified otherwise						
Hyperlipidemia	1,452 (35.1)	11,147 (44.9)	-20.1	1,443 (35.0)	1,427 (34.6)	0.8
Diabetes mellitus	605 (14.6)	3,353 (13.5)	3.2	603 (14.6)	607 (14.7)	-0.3
Hypertension	1,946 (47.0)	12,331 (49.6)	-5.3	1,939 (47.1)	1,963 (47.6)	-1.2
Heart failure	353 (8.5)	1,600 (6.4)	7.9	349 (8.5)	348 (8.4)	0.1
Atrial fibrillation	449 (10.8)	2,033 (8.2)	9.1	443 (10.7)	429 (10.4)	1.1
Ischemic heart disease	1,912 (46.2)	9,147 (36.8)	19.1	1,904 (46.2)	1877 (45.5)	1.3
Peripheral arterial disease	258 (6.2)	1,352 (5.4)	3.4	258 (6.3)	249 (6.0)	0.9
Hemorrhagic stroke	85 (2.1)	495 (2.0)	0.4	84 (2.0)	71 (1.7)	2.3
Ischemic stroke	1,912 (46.2)	15,252 (61.4)	-30.9	1,904 (46.2)	1,865 (45.3)	1.9
Myocardial infarction	2,438 (58.9)	10,502 (42.3)	33.7	2,427 (58.9)	2,441 (59.2)	-0.7
Chronic kidney disease	269 (6.5)	2,486 (10.0)	-12.8	264 (6.4)	246 (6.0)	1.8
Severe liver impairment	5 (0.1)	48 (0.2)	-1.8	5 (0.1)	5 (0.1)	0.0
Hypothyroidism	218 (5.3)	1,614 (6.5)	-5.2	215 (5.2)	202 (4.9)	1.4
Hyperthyroidism	57 (1.4)	440 (1.8)	-3.2	56 (1.4)	58 (1.4)	-0.4
Rheumatoid Arthritis	96 (2.3)	519 (2.1)	1.6	95 (2.3)	92 (2.2)	0.5
Osteoarthritis	881 (21.3)	5,442 (21.9)	-1.5	877 (21.3)	844 (20.5)	2.0
Pre-existing muscle complaints	373 (9.0)	2,439 (9.8)	-2.8	371 (9.0)	371 (9.0)	0.0
Musculoskeletal injuries	1,169 (28.2)	7,311 (29.4)	-2.6	1,164 (28.2)	1,111 (27.0)	2.9
Chronic obstructive pulmonary disease	264 (6.4)	1,644 (6.6)	-1.0	263 (6.4)	249 (6.0)	1.4
Macular degeneration	49 (1.2)	351 (1.4)	-2.0	48 (1.2)	59 (1.4)	-2.4
Falls†	159 (3.8)	1,220 (4.9)	-5.2	157 (3.8)	155 (3.8)	0.3
Pressure ulcer†	30 (0.7)	167 (0.7)	0.6	30 (0.7)	34 (0.8)	-1.1
Incontinence†	55 (1.3)	381 (1.5)	-1.7	55 (1.3)	44 (1.1)	2.5
Peripheral venous thrombosis†	76 (1.8)	424 (1.7)	1.0	76 (1.8)	79 (1.9)	-0.5
Pneumonia†	39 (0.9)	247 (1.0)	-0.5	39 (0.9)	40 (1.0)	-0.2

Dysphagia†	33 (0.8)	212 (0.9)	-0.6	33 (0.8)	22 (0.5)	3.3
Anemia†	114 (2.8)	739 (3.0)	-1.3	113 (2.7)	130 (3.2)	-2.4
Comedication, n (%) - in the 180 days before the cohort entry date						
Fibrates	63 (1.5)	268 (1.1)	3.9	62 (1.5)	65 (1.6)	-0.6
Amiodarone	121 (2.9)	542 (2.2)	4.7	120 (2.9)	102 (2.5)	2.7
Systemic corticosteroids	192 (4.6)	960 (3.9)	3.8	190 (4.6)	171 (4.1)	2.3
Antipsychotics	15 (0.4)	151 (0.6)	-3.5	15 (0.4)	12 (0.3)	1.3
H_2-receptor antagonists	352 (8.5)	1,430 (5.8)	10.7	352 (8.5)	367 (8.9)	-1.3
Benzodiazepines	452 (10.9)	2,269 (9.1)	5.9	449 (10.9)	434 (10.5)	1.2
Number of cardiovascular drug classes						
0	130 (3.1)	1,388 (5.6)	-12.0	129 (3.1)	120 (2.9)	1.3
1 to 3	2,300 (55.6)	16,207 (65.3)	-19.9	2,288 (55.5)	2,301 (55.8)	-0.6
4 to 10	1,709 (41.3)	7,241 (29.2)	25.6	1,704 (41.3)	1,700 (41.3)	0.2
Number of general practitioner visits‡, mean (SD)	20.5 (13.6)	21.7 (14.0)	-9.0	20.4 (13.5)	20.4 (13.7)	-0.2
Hospitalization†, n (%)	1,548 (37.4)	8,440 (34.0)	7.1	1,535 (37.2)	1,548 (37.6)	-0.7
Daily statin dose [mg], n (%)						
20 (pravastatin) vs 10 (simvastatin)	1,348 (32.6)	8,349 (33.6)	-2.2	1,338 (32.5)	1,329 (32.2)	0.5
40 (pravastatin) vs 20 (simvastatin)	2,791 (67.4)	16,487 (66.4)	2.2	2,783 (67.5)	2,792 (67.8)	-0.5
Cohort entry date, n (%)						
2000-2001	1,617 (39.1)	6,222 (25.1)	30.4	1,617 (39.2)	1,617 (39.2)	0.0
2002-2003	1,821 (44.0)	6,909 (27.8)	34.2	1,821 (44.2)	1,821 (44.2)	0.0
2004-2005	500 (12.1)	5,975 (24.1)	-31.5	500 (12.1)	500 (12.1)	0.0
2006-2007	72 (1.7)	2,983 (12.0)	-41.5	71 (1.7)	71 (1.7)	0.0
2008-2009	47 (1.1)	1,257 (5.1)	-22.8	44 (1.1)	44 (1.1)	0.0
2010-2011	49 (1.2)	602 (2.4)	-9.3	44 (1.1)	44 (1.1)	0.0
2012-2013	22 (0.5)	519 (2.1)	-13.7	21 (0.5)	21 (0.5)	0.0
2014-2015	7 (0.2)	289 (1.2)	-12.2	X	X	X
2016-2017	X	80 (0.3)	X	0	0	0.0

SD standard deviation; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

* Last record before the cohort entry date.

† Assessed in the 3 years before the cohort entry date.

‡ Assessed in the 1 year before the cohort entry date

Appendix Table 6. Baseline covariates of users of rosuvastatin 5-40 mg and atorvastatin 10-80 mg (moderate- to high-intensity statin therapy) in the secondary prevention cohort before and after propensity score matching

	Cohort before propensity score matching			Cohort after propensity score matching		
Covariate	**Rosuvastatin N = 891**	**Atorvastatin N = 18,000**	**Absolute standardized difference (%)**	**Rosuvastatin N = 836**	**Atorvastatin N = 836**	**Absolute standardized difference (%)**
Age [years], mean (SD)	66.6 (9.6)	63.4 (10.5)	31.4	66.6 (9.5)	66.7 (9.6)	-1.5
Male, n (%)	516 (57.9)	11,536 (64.1)	-12.7	482 (57.7)	461 (55.1)	5.1
Current smoker*, n (%)	209 (23.5)	4,791 (26.6)	-7.3	198 (23.7)	200 (23.9)	-0.6
>14 units of alcohol per week*, n (%)	79 (8.9)	1,847 (10.3)	-4.7	72 (8.6)	67 (8.0)	2.2
Obesity*, n (%)	223 (25.0)	4,407 (24.5)	1.3	206 (24.6)	191 (22.8)	4.2
Comorbidities, n (%) - at any time before the cohort entry date, if not specified otherwise						
Hyperlipidemia	460 (51.6)	8,312 (46.2)	10.9	428 (51.2)	426 (51.0)	0.5
Diabetes mellitus	112 (12.6)	1,807 (10.0)	8.0	105 (12.6)	104 (12.4)	0.4
Hypertension	447 (50.2)	6,939 (38.6)	23.5	421 (50.4)	430 (51.4)	-2.2
Heart failure	51 (5.7)	961 (5.3)	1.7	45 (5.4)	51 (6.1)	-3.1
Atrial fibrillation	85 (9.5)	1,212 (6.7)	10.3	76 (9.1)	83 (9.9)	-2.9
Ischemic heart disease	328 (36.8)	6,711 (37.3)	-1.0	300 (35.9)	313 (37.4)	-3.2
Peripheral arterial disease	45 (5.1)	479 (2.7)	12.4	44 (5.3)	44 (5.3)	0.0
Hemorrhagic stroke	16 (1.8)	269 (1.5)	2.4	16 (1.9)	12 (1.4)	3.7
Ischemic stroke	537 (60.3)	7,740 (43.0)	35.1	506 (60.5)	511 (61.1)	-1.2
Myocardial infarction	381 (42.8)	10,647 (59.2)	-33.2	353 (42.2)	347 (41.5)	1.5
Chronic kidney disease	90 (10.1)	1,506 (8.4)	6.0	82 (9.8)	75 (9.0)	2.9
Severe liver impairment	X	23 (0.1)	X	X	X	X
Hypothyroidism	59 (6.6)	1,017 (5.7)	4.1	54 (6.5)	52 (6.2)	1.0
Hyperthyroidism	22 (2.5)	255 (1.4)	7.6	20 (2.4)	20 (2.4)	0.0
Rheumatoid Arthritis	19 (2.1)	380 (2.1)	0.1	18 (2.2)	18 (2.2)	0.0
Osteoarthritis	205 (23.0)	3,454 (19.2)	9.4	196 (23.4)	204 (24.4)	-2.2
Pre-existing muscle complaints	98 (11.0)	1,802 (10.0)	3.2	91 (10.9)	91 (10.9)	0.0
Musculoskeletal injuries	285 (32.0)	6,358 (35.3)	-7.1	266 (31.8)	270 (32.3)	-1.0
Chronic obstructive pulmonary disease	53 (5.9)	1,075 (6.0)	-0.1	48 (5.7)	47 (5.6)	0.5
Macular degeneration	8 (0.9)	149 (0.8)	0.8	7 (0.8)	8 (1.0)	-1.3
Falls†	42 (4.7)	656 (3.6)	5.3	38 (4.5)	30 (3.6)	4.8
Pressure ulcer†	X	115 (0.6)	X	X	7 (0.8)	X
Incontinence†	7 (0.8)	209 (1.2)	-3.8	7 (0.8)	7 (0.8)	0.0
Peripheral venous thrombosis†	19 (2.1)	287 (1.6)	4.0	15 (1.8)	14 (1.7)	0.9

Pneumonia†	10 (1.1)	194 (1.1)	0.4	8 (1.0)	6 (0.7)	2.6
Dysphagia†	9 (1.0)	129 (0.7)	3.2	6 (0.7)	8 (1.0)	-2.6
Anemia†	21 (2.4)	466 (2.6)	-1.5	21 (2.5)	19 (2.3)	1.6
Comedication, n (%) - in the 180 days before the cohort entry date						
Fibrates	25 (2.8)	170 (0.9)	13.8	22 (2.6)	24 (2.9)	-1.5
Amiodarone	13 (1.5)	275 (1.5)	-0.6	13 (1.6)	15 (1.8)	-1.9
Systemic corticosteroids	40 (4.5)	836 (4.6)	-0.7	37 (4.4)	28 (3.3)	5.6
Antipsychotics	8 (0.9)	108 (0.6)	3.5	6 (0.7)	10 (1.2)	-4.9
H_2-receptor antagonists	36 (4.0)	944 (5.2)	-5.7	32 (3.8)	26 (3.1)	3.9
Benzodiazepines	95 (10.7)	1,414 (7.9)	9.7	92 (11.0)	88 (10.5)	1.5
Number of cardiovascular drug classes						
0	68 (7.6)	711 (4.0)	15.8	63 (7.5)	67 (8.0)	-1.8
1 to 3	560 (62.9)	10,630 (59.1)	7.8	525 (62.8)	510 (61.0)	3.7
4 to 10	263 (29.5)	6,659 (37.0)	-15.9	248 (29.7)	259 (31.0)	-2.9
Number of general practitioner visits‡, mean (SD)	22.4 (14.4)	20.8 (15.0)	10.3	22.1 (14.2)	21.9 (14.2)	1.3
Hospitalization†, n (%)	303 (34.0)	9,760 (54.2)	-41.6	285 (34.1)	275 (32.9)	2.5
Daily statin dose [mg], n (%)						
5 (rosuvastatin) vs 10 (atorvastatin)	69 (7.7)	5,264 (29.2)	-57.6	61 (7.3)	64 (7.7)	-1.4
10 (rosuvastatin) vs 20 (atorvastatin)	777 (87.2)	2,990 (16.6)	199.6	730 (87.3)	727 (87.0)	1.1
20 (rosuvastatin) vs 40 (atorvastatin)	35 (3.9)	3,903 (21.7)	-55.1	35 (4.2)	35 (4.2)	0.0
40 (rosuvastatin) vs 80 (atorvastatin)	10 (1.1)	5,843 (32.5)	-92.3	10 (1.2)	10 (1.2)	0.0
Cohort entry date, n (%)						
2000-2001	NA	NA		NA	NA	
2002-2003	211 (23.7)	2,203 (12.2)	30.1	195 (23.3)	195 (23.3)	0.0
2004-2005	389 (43.7)	4,622 (25.7)	38.5	384 (45.9)	384 (45.9)	0.0
2006-2007	126 (14.1)	1,394 (7.7)	20.6	121 (14.5)	121 (14.5)	0.0
2008-2009	63 (7.1)	1,040 (5.8)	5.3	53 (6.3)	53 (6.3)	0.0
2010-2011	42 (4.7)	1,563 (8.7)	-15.9	32 (3.8)	32 (3.8)	0.0
2012-2013	27 (3.0)	2,220 (12.3)	-35.5	22 (2.6)	22 (2.6)	0.0
2014-2015	14 (1.6)	2,786 (15.5)	-51.4	14 (1.7)	14 (1.7)	0.0
2016-2017	19 (2.1)	2,172 (12.1)	-39.4	15 (1.8)	15 (1.8)	0.0

SD standard deviation; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality); *NA* not applicable

* Last record before the cohort entry date.

† Assessed in the 3 years before the cohort entry date.

‡ Assessed in the 1 year before the cohort entry date.

Appendix Table 7. Baseline covariates of users of simvastatin 40-80 mg and atorvastatin 10-20 mg (moderate- to high-intensity statin therapy) in the secondary prevention cohort before and after propensity score matching

	Cohort before propensity score matching			Cohort after propensity score matching		
Covariate	**Simvastatin N = 28,142**	**Atorvastatin N = 15,404**	**Absolute standardized difference (%)**	**Simvastatin N = 6,716**	**Atorvastatin N = 6,716**	**Absolute standardized difference (%)**
Age [years], mean (SD)	64.8 (10.3)	66.6 (9.3)	-18.1	66.9 (9.5)	66.8 (9.5)	0.8
Male, n (%)	17,169 (61.0)	9,138 (59.3)	3.4	4,064 (60.5)	4,016 (59.8)	1.5
Current smoker*, n (%)	7,267 (25.8)	3,483 (22.6)	7.5	1,571 (23.4)	1,566 (23.3)	0.2
>14 units of alcohol per week*, n (%)	2,854 (10.1)	1,367 (8.9)	4.3	615 (9.2)	594 (8.8)	1.1
Obesity*, n (%)	6,358 (22.6)	3,422 (22.2)	0.9	1,444 (21.5)	1,418 (21.1)	0.9
Comorbidities, n (%) - at any time before the cohort entry date, if not specified otherwise						
Hyperlipidemia	11,229 (39.9)	7,098 (46.1)	-12.5	2,886 (43.0)	2,892 (43.1)	-0.2
Diabetes mellitus	2,354 (8.4)	2,527 (16.4)	-24.6	1,004 (14.9)	974 (14.5)	1.3
Hypertension	11,331 (40.3)	7,657 (49.7)	-19.1	3,338 (49.7)	3,305 (49.2)	1.0
Heart failure	1,135 (4.0)	1,080 (7.0)	-13.1	443 (6.6)	449 (6.7)	-0.4
Atrial fibrillation	2,185 (7.8)	1,279 (8.3)	-2.0	577 (8.6)	564 (8.4)	0.7
Ischemic heart disease	7,229 (25.7)	6,159 (40.0)	-30.8	2,407 (35.8)	2,410 (35.9)	-0.1
Peripheral arterial disease	765 (2.7)	861 (5.6)	-14.4	334 (5.0)	331 (4.9)	0.2
Hemorrhagic stroke	496 (1.8)	283 (1.8)	-0.6	142 (2.1)	135 (2.0)	0.7
Ischemic stroke	17,304 (61.5)	9,117 (59.2)	4.7	4,116 (61.3)	4,113 (61.2)	0.1
Myocardial infarction	11,418 (40.6)	6,932 (45.0)	-9.0	2,855 (42.5)	2,862 (42.6)	-0.2
Chronic kidney disease	2,587 (9.2)	1,332 (8.7)	1.9	672 (10.0)	689 (10.3)	-0.8
Severe liver impairment	60 (0.2)	18 (0.1)	2.4	13 (0.2)	9 (0.1)	1.5
Hypothyroidism	1,688 (6.0)	978 (6.4)	-1.5	420 (6.3)	411 (6.1)	0.6
Hyperthyroidism	464 (1.7)	279 (1.8)	-1.2	105 (1.6)	118 (1.8)	-1.5
Rheumatoid Arthritis	602 (2.1)	343 (2.2)	-0.6	159 (2.4)	153 (2.3)	0.6
Osteoarthritis	5,978 (21.2)	3,335 (21.7)	-1.0	1,491 (22.2)	1,505 (22.4)	-0.5
Pre-existing muscle complaints	2,788 (9.9)	1,559 (10.1)	-0.7	695 (10.3)	696 (10.4)	-0.0
Musculoskeletal injuries	9,576 (34.0)	4,629 (30.1)	8.5	2,081 (31.0)	2,083 (31.0)	-0.1
Chronic obstructive pulmonary disease	1,918 (6.8)	938 (6.1)	3.0	464 (6.9)	455 (6.8)	0.5
Macular degeneration	286 (1.0)	170 (1.1)	-0.9	79 (1.2)	71 (1.1)	1.1
Falls†	1,332 (4.7)	715 (4.6)	0.4	345 (5.1)	359 (5.3)	-0.9
Pressure ulcer†	183 (0.7)	127 (0.8)	-2.0	49 (0.7)	49 (0.7)	0.0
Incontinence†	372 (1.3)	202 (1.3)	0.1	97 (1.4)	103 (1.5)	-0.7
Peripheral venous thrombosis†	430 (1.5)	261 (1.7)	-1.3	115 (1.7)	129 (1.9)	-1.6

Pneumonia†	329 (1.2)	160 (1.0)	1.2	77 (1.1)	78 (1.2)	-0.1
Dysphagia†	269 (1.0)	129 (0.8)	1.3	56 (0.8)	60 (0.9)	-0.6
Anemia†	743 (2.6)	449 (2.9)	-1.7	201 (3.0)	208 (3.1)	-0.6
Comedication, n (%) - in the 180 days before the cohort entry date						
Fibrates	169 (0.6)	348 (2.3)	-14.0	81 (1.2)	85 (1.3)	-0.5
Amiodarone	257 (0.9)	334 (2.2)	-10.2	134 (2.0)	134 (2.0)	0.0
Systemic corticosteroids	1,388 (4.9)	641 (4.2)	3.7	300 (4.5)	295 (4.4)	0.4
Antipsychotics	194 (0.7)	88 (0.6)	1.5	43 (0.6)	45 (0.7)	-0.4
H_2-receptor antagonists	1,118 (4.0)	899 (5.8)	-8.6	324 (4.8)	306 (4.6)	1.3
Benzodiazepines	2,295 (8.2)	1,476 (9.6)	-5.0	663 (9.9)	636 (9.5)	1.4
Number of cardiovascular drug classes						
0	1,120 (4.0)	884 (5.7)	-8.2	330 (4.9)	347 (5.2)	-1.2
1 to 3	18,917 (67.2)	9,763 (63.4)	8.1	4,223 (62.9)	4,209 (62.7)	0.4
4 to 10	8,105 (28.8)	4,757 (30.9)	-4.5	2,163 (32.2)	2,160 (32.2)	0.1
Number of general practitioner visits‡, mean (SD)	21.0 (14.6)	21.5 (14.0)	-3.5	21.8 (14.4)	21.9 (14.0)	-0.4
Hospitalization†, n (%)	14,699 (52.2)	5,376 (34.9)	35.5	2,439 (36.3)	2,453 (36.5)	-0.4
Daily statin dose [mg], n (%)						
40 (simvastatin) vs 10 (atorvastatin)	3,917 (25.4)	11,487 (74.6)	80.5	6,613 (98.5)	6,614 (98.5)	-0.1
80 (simvastatin) vs 20 (atorvastatin)	110 (0.4)	28,032 (99.6)	-80.5	103 (1.5)	102 (1.5)	0.1
Cohort entry date, n (%)						
2000-2001	229 (0.8)	4,158 (27.0)	-81.7	229 (3.4)	229 (3.4)	0.0
2002-2003	3,216 (11.4)	5,080 (33.0)	-53.7	2,877 (42.8)	2,877 (42.8)	0.0
2004-2005	5,058 (18.0)	3,811 (24.7)	-16.6	2,630 (39.2)	2,630 (39.2)	0.0
2006-2007	5,479 (19.5)	625 (4.1)	49.3	342 (5.1)	342 (5.1)	0.0
2008-2009	5,307 (18.9)	152 (1.0)	62.6	101 (1.5)	101 (1.5)	0.0
2010-2011	4,278 (15.2)	114 (0.7)	55.4	71 (1.1)	71 (1.1)	0.0
2012-2013	3,027 (10.8)	402 (2.6)	33.1	189 (2.8)	189 (2.8)	0.0
2014-2015	1,250 (4.4)	656 (4.3)	0.9	198 (2.9)	198 (2.9)	0.0
2016-2017	298 (1.1)	406 (2.6)	-11.7	79 (1.2)	79 (1.2)	0.0

SD standard deviation

* Last record before the cohort entry date.

† Assessed in the 3 years before the cohort entry date.

‡ Assessed in the 1 year before the cohort entry date.

Appendix Table 8. Censoring reasons and duration of follow-up for the secondary prevention cohorts before and after propensity score matching

	Low-intensity statin therapy		Moderate- to high-intensity statin therapy			
	Pravastatin 20-40 mg	**Simvastatin 10-20 mg**	**Rosuvastatin 5-40 mg**	**Atorvastatin 10-80 mg**	**Simvastatin 40-80 mg**	**Atorvastatin 10-20 mg**
Before propensity score matching	**N = 4,139**	**N = 24,836**	**N = 891**	**N = 18,000**	**N = 28,142**	**N = 15,404**
Censoring reasons, n (%)						
Muscular event (Outcome)	43 (1.0)	276 (1.1)	14 (1.6)	259 (1.4)	467 (1.7)	145 (0.9)
Recording of statin intolerance	7 (0.2)	187 (0.8)	5 (0.6)	80 (0.4)	206 (0.7)	60 (0.4)
Treatment switch	547 (13.2)	1,732 (7.0)	73 (8.2)	1,345 (7.5)	2,744 (9.8)	1,098 (7.1)
Discontinuation of statin treatment	426 (10.3)	3,928 (15.8)	127 (14.3)	1,688 (9.4)	3,016 (10.7)	2,182 (14.2)
Death	40 (1.0)	191 (0.8)	5 (0.6)	134 (0.7)	239 (0.8)	114 (0.7)
Recording of an exclusion criterion	90 (2.2)	586 (2.4)	28 (3.1)	384 (2.1)	756 (2.7)	311 (2.0)
End of study enrollment	2,986 (72.1)	17,936 (72.2)	639 (71.7)	14,110 (78.4)	20,714 (73.6)	11,494 (74.6)
Duration of follow-up						
Mean number of days (standard deviation)	302.9 (105.8)	301.8 (105.9)	299.9 (107.0)	297.2 (109.7)	300.2 (108.9)	304.8 (104.1)
Median number of days (interquartile range)	365 (259-365)	365 (251-365)	365 (236-365)	365 (237-365)	365 (250-365)	365 (266-365)
After propensity score matching	**N = 4,121**	**N = 4,121**	**N = 836**	**N = 836**	**N = 6,716**	**N = 6,716**
Censoring reasons, n (%)						
Muscular event (Outcome)	43 (1.0)	42 (1.0)	13 (1.6)	14 (1.7)	95 (1.4)	66 (1.0)
Recording of statin intolerance	7 (0.2)	15 (0.4)	5 (0.6)	X	47 (0.7)	43 (0.6)
Treatment switch	546 (13.2)	286 (6.9)	69 (8.3)	65 (7.8)	528 (7.9)	580 (8.6)
Discontinuation of statin treatment	423 (10.3)	556 (13.5)	120 (14.4)	116 (13.9)	750 (11.2)	1,007 (15.0)
Death	40 (1.0)	37 (0.9)	X	5 (0.6)	83 (1.2)	58 (0.9)
Recording of an exclusion criterion	89 (2.2)	92 (2.2)	24 (2.9)	11 (1.3)	188 (2.8)	158 (2.4)
End of study enrollment	2,973 (72.1)	3,093 (75.1)	601 (71.9)	623 (74.5)	5,025 (74.8)	4,804 (71.5)
Duration of follow-up						
Mean number of days (standard deviation)	303.0 (105.8)	307.7 (102.6)	299.8 (107.3)	304.8 (105.8)	306.1 (104.0)	302.0 (105.1)
Median number of days (interquartile range)	365 (260-365)	365 (286-365)	365 (237-365)	365 (271-365)	365 (278-365)	365 (254-365)

X cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

Appendix Table 9. Baseline covariates by treatment group in the primary prevention cohorts of pravastatin vs simvastatin and rosuvastatin vs atorvastatin before propensity score matching (simvastatin vs atorvastatin in Appendix Table 4)

	Low-intensity statin therapy			Moderate- to high-intensity statin therapy		
Covariate	**Pravastatin N = 9,710**	**Simvastatin N = 179,416**	**ASD (%)**	**Rosuvastatin N = 7,057**	**Atorvastatin N = 85,699**	**ASD (%)**
Age [years], mean (SD)	63.1 (9.8)	62.5 (9.7)	6.1	61.0 (9.9)	61.4 (9.9)	-4.3
Male, n (%)	4,891 (50.4)	86,857 (48.4)	3.9	3,427 (48.6)	42,933 (50.1)	-3.1
Current smoker*, n (%)	1,950 (20.1)	34,159 (19.0)	2.6	1,381 (19.6)	16,019 (18.7)	2.2
>14 alcohol units/week*, n (%)	809 (8.3)	17,594 (9.8)	-5.1	710 (10.1)	8,899 (10.4)	-1.1
Obesity*, n (%)	2,533 (26.1)	53,936 (30.1)	-8.9	2,111 (29.9)	28,427 (33.2)	-7.0
Comorbidities, n (%) - at any time before the cohort entry date, if not specified otherwise						
Hyperlipidemia	4,916 (50.6)	123,363 (68.8)	-37.6	4,894 (69.3)	61,575 (71.9)	-5.5
Diabetes mellitus	2,099 (21.6)	38,844 (21.7)	-0.1	1,507 (21.4)	19,503 (22.8)	-3.4
Hypertension	4,751 (48.9)	93,197 (51.9)	-6.0	3,626 (51.4)	41,032 (47.9)	7.0
Heart failure	401 (4.1)	2,879 (1.6)	15.2	116 (1.6)	1,406 (1.6)	0.0
Atrial fibrillation	793 (8.2)	6,101 (3.4)	20.5	217 (3.1)	3,466 (4.0)	-5.2
Ischemic heart disease	2,629 (27.1)	18,479 (10.3)	44.1	700 (9.9)	8,602 (10.0)	-0.4
Peripheral arterial disease	492 (5.1)	4,541 (2.5)	13.3	148 (2.1)	1,788 (2.1)	0.1
Hemorrhagic stroke	83 (0.9)	1,029 (0.6)	3.3	31 (0.4)	550 (0.6)	-2.8
Chronic kidney disease	578 (6.0)	15,871 (8.8)	-11.1	483 (6.8)	6,617 (7.7)	-3.4
Severe liver impairment	30 (0.3)	230 (0.1)	3.9	6 (0.1)	136 (0.2)	-2.1
Hypothyroidism	658 (6.8)	13,649 (7.6)	-3.2	522 (7.4)	6,545 (7.6)	-0.9
Hyperthyroidism	161 (1.7)	3,042 (1.7)	-0.3	104 (1.5)	1,460 (1.7)	-1.8
Rheumatoid Arthritis	166 (1.7)	2,742 (1.5)	1.4	100 (1.4)	1,459 (1.7)	-2.3
Osteoarthritis	1,863 (19.2)	34,841 (19.4)	-0.6	1,251 (17.7)	16,424 (19.2)	-3.7
Pre-existing muscle Complaints	844 (8.7)	16,034 (8.9)	-0.9	576 (8.2)	8,716 (10.2)	-7.0
Musculoskeletal injuries	2,823 (29.1)	56,962 (31.7)	-5.8	2,150 (30.5)	29,770 (34.7)	-9.1
COPD	439 (4.5)	7,030 (3.9)	3.0	231 (3.3)	3,563 (4.2)	-4.7
Macular degeneration	84 (0.9)	1,381(0.8)	1.1	37 (0.5)	577 (0.7)	-1.9
Falls†	266 (2.7)	5,462 (3.0)	-1.8	175 (2.5)	2,476 (2.9)	-2.5
Pressure ulcer†	54 (0.6)	723 (0.4)	2.2	26 (0.4)	335 (0.4)	-0.4
Incontinence†	70 (0.7)	1,645 (0.9)	-2.2	53 (0.8)	849 (1.0)	-2.6
Peripheral venous thrombosis†	155 (1.6)	2,297 (1.3)	2.7	98 (1.4)	1,069 (1.2)	1.2
Pneumonia†	66 (0.7)	868 (0.5)	2.6	31 (0.4)	480 (0.6)	-1.7
Dysphagia†	65 (0.7)	1,078 (0.6)	0.9	33 (0.5)	486 (0.6)	-1.4
Anemia†	207 (2.1)	3,485 (1.9)	1.3	94 (1.3)	1,604 (1.9)	-4.3
Comedication, n (%) - in the 180 days before the cohort entry date						
Fibrates	132 (1.4)	1,243 (0.7)	6.6	180 (2.6)	818 (1.0)	12.2
Amiodarone	185 (1.9)	930 (0.5)	12.7	21 (0.3)	466 (0.5)	-3.8
Systemic corticosteroids	384 (4.0)	5,636 (3.1)	4.4	218 (3.1)	3,385 (3.9)	-4.7
Antipsychotics	41 (0.4)	1,135 (0.6)	-2.9	47 (0.7)	559 (0.7)	0.2
H_2-receptor antagonists	539 (5.6)	5,731 (3.2)	11.5	199 (2.8)	2,579 (3.0)	-1.1
Benzodiazepines	844 (8.7)	11,841 (6.6)	7.9	530 (7.5)	5,630 (6.6)	3.7
Number of cardiovascular drug classes						
0	1,760 (18.1)	52,934 (29.5)	-27.0	2,248 (31.9)	27,468 (32.1)	-0.4
1 to 3	5,810 (59.8)	108,015 (60.2)	-0.8	4,077 (57.8)	49,323 (57.6)	0.4
4 to 10	2,140 (22.0)	18,467 (10.3)	32.3	732 (10.4)	8,908 (10.4)	-0.1
Number of general practitioner visits‡, mean (SD)	20.6 (13.5)	19.6 (12.3)	7.6	19.1 (12.2)	20.8 (13.5)	-13.3
Hospitalization†, n (%)	2,748 (28.3)	47,739 (26.6)	3.8	1,735 (24.6)	29,538 (34.5)	-21.8

Daily statin dose [mg], n (%)						
20 (P), 10 (S)	4,412 (45.4)	50,581 (28.2)	36.3	NA	NA	
40 (P), 20 (S)	5,298 (54.6)	128,835 (71.8)	-36.3	NA	NA	
40 (S), 5 (R), 10 (A)	NA	NA		696 (9.9)	42,765 (49.9)	-97.3
80 (S), 10 (R), 20 (A)	NA	NA		6,112 (86.6)	32,558 (38.0)	116.0
20 (R), 40 (A)	NA	NA		226 (3.2)	8,440 (9.8)	-27.2
40 (R), 80 (A)	NA	NA		23 (0.3)	1,936 (2.3)	-17.2
Cohort entry date, n (%)						
2000-2001	2,912 (30.0)	14,676 (8.2)	57.8	NA	NA	
2002-2003	4,202 (43.3)	25,378 (14.1)	68.0	1,425 (20.2)	11,078 (12.9)	19.6
2004-2005	1,409 (14.5)	39,146 (21.8)	-19.0	3,132 (44.4)	25,631 (29.9)	30.3
2006-2007	322 (3.3)	43,099 (24.0)	-63.2	1,263 (17.9)	6,664 (7.8)	30.6
2008-2009	216 (2.2)	25,547 (14.2)	-44.8	557 (7.9)	1,994 (2.3)	25.5
2010-2011	246 (2.5)	13,840 (7.7)	-23.7	344 (4.9)	1,560 (1.8)	17.0
2012-2013	284 (2.9)	11,139 (6.2)	-15.8	147 (2.1)	7,916 (9.2)	-31.3
2014-2015	89 (0.9)	5,010 (2.8)	-13.9	110 (1.6)	16,239 (18.9)	-59.8
2016-2017	30 (0.3)	1,581 (0.9)	-7.4	79 (1.1)	14,617 (17.1)	-57.7

ASD absolute standardized difference; *SD* standard deviation; *COPD* chronic obstructive pulmonary disease; *P* pravastatin; *S* simvastatin; *R* rosuvastatin; *A* atorvastatin; *NA* not applicable

* Last record before the cohort entry date.

† Assessed in the 3 years before the cohort entry date.

‡ Assessed in the 1 year before the cohort entry date.

Appendix Table 10. Censoring reasons and duration of follow-up for the primary prevention cohorts before propensity score matching

	Low-intensity statin therapy		Moderate- to high-intensity statin therapy			
	Pravastatin 20-40 mg N = 9,710	Simvastatin 10-20 mg N = 179,416	Rosuvastatin 5-40 mg N = 7,057	Atorvastatin 10-80 mg N = 85,699	Simvastatin 40-80 mg N = 161,572	Atorvastatin 10-20 mg N = 101,359
Censoring reasons, n (%)						
Muscular event (Outcome)	82 (0.8)	2,205 (1.2)	101 (1.4)	854 (1.0)	2,456 (1.5)	957 (0.9)
Recording of statin intolerance	17 (0.2)	1,254 (0.7)	20 (0.3)	340 (0.4)	1,155 (0.7)	313 (0.3)
Treatment switch	1,287 (13.3)	12,302 (6.9)	682 (9.7)	5,995 (7.0)	14,222 (8.8)	6,828 (6.7)
Discontinuation of statin treatment	1,760 (18.1)	38,286 (21.3)	1,414 (20.0)	16,801 (19.6)	35,060 (21.7)	19,802 (19.5)
Death	40 (0.4)	385 (0.2)	8 (0.1)	179 (0.2)	416 (0.3)	199 (0.2)
Recording of an exclusion criterion	198 (2.0)	3,022 (1.7)	126 (1.8)	1,465 (1.7)	3,002 (1.9)	1,696 (1.7)
Myocardial infarction or ischemic stroke	283 (2.9)	2,156 (1.2)	59 (0.8)	1,152 (1.3)	2,429 (1.5)	1,278 (1.3)
End of study enrollment	6,043 (62.2)	119,806 (66.8)	4,647 (65.8)	58,913 (68.7)	102,832 (63.6)	70,286 (69.3)
Duration of follow-up						
Mean number of days (standard deviation)	285.1 (112.4)	291.4 (109.7)	292.1 (110.4)	274.2 (117.0)	281.4 (114.9)	283.4 (113.2)
Median number of days (interquartile range)	365 (184-365)	365 (202-365)	365 (205-365)	365 (155-365)	365 (174-365)	365 (176-365)

Appendix Table 11. Hazard ratios for muscular events in the primary prevention cohorts before propensity score matching, using multivariable logistic regression models

	Number of events		Total person-years of follow-up		HR (95% CI)	
	Exposed	Comparator	Exposed	Comparator	Crude	Adjusted
Low-intensity statin therapy						
Pravastatin vs Simvastatin (ref)						
Overall	82 (0.8)	2,205 (1.2)	7,584	143,220	0.70 (0.56-0.87)	0.87 (0.69-1.09)
Subgroup analyses						
Male	33	955	3,868	69,725	0.62 (0.44-0.88)	0.75 (0.53-1.08)
Female	49	1,250	3,716	73,496	0.77 (0.58-1.02)	0.96 (0.71-1.29)
40-64 years	39	1,211	3,913	78,433	0.64 (0.47-0.88)	0.76 (0.55-1.06)
≥65 years	43	994	3,671	64,787	0.76 (0.56-1.03)	0.98 (0.71-1.34)
20 vs 10 mg	35	567	3,470	40,673	0.72 (0.51-1.01)	0.79 (0.56-1.12)
40 vs 20 mg	47	1,638	4,114	102,547	0.71 (0.53-0.95)	0.95 (0.70-1.29)
Sensitivity analyses						
No muscle complaints before CED	71	1,833	6,937	130,826	0.73 (0.57-0.92)	0.93 (0.72-1.19)
No use of CYP3A4 inhibiting drugs*	57	1,664	5,277	106,909	0.69 (0.53-0.90)	0.86 (0.65-1.13)

Additional analyses						
Censoring if dosage change	75	1,948	7,040	127,017	0.70 (0.56-0.88)	0.86 (0.68-1.09)
Broader outcome definition†	99	3,459	7,584	143,220	0.54 (0.44-0.66)	0.74 (0.60-0.91)
Moderate- to high-intensity statin therapy						
Rosuvastatin vs Atorvastatin (ref)						
Overall	101 (1.4)	854 (1.0)	5,648	64,369	1.36 (1.11-1.68)	1.28 (1.02-1.61)
Subgroup analyses						
Male	42	357	2,776	32,408	1.39 (1.01-1.91)	1.22 (0.86-1.75)
Female	59	497	2,872	31,961	1.34 (1.02-1.75)	1.32 (0.97-1.78)
40-64 years	59	496	3,475	38,095	1.32 (1.01-1.73)	1.19 (0.88-1.60)
≥65 years	42	358	2,173	26,274	1.43 (1.04-1.97)	1.44 (1.00-2.07)
5-10 vs 10-20 mg	97	725	5,452	56,895	1.41 (1.14-1.75)	1.28 (1.01-1.63)
20-40 vs 40-80 mg	X	129	196	7,474	1.20 (0.44-3.25)	1.07 (0.39-2.95)
Sensitivity analyses						
No muscle complaints before CED	88	692	5,198	58,043	1.44 (1.15-1.79)	1.35 (1.05-1.73)
No use of CYP3A4 inhibiting drugs*	79	638	4,477	47,122	1.32 (1.04-1.67)	1.29 (0.99-1.67)
Additional analyses						
Censoring if dosage change	97	803	5,412	59,768	1.36 (1.10-1.68)	1.25 (0.98-1.58)
Broader outcome definition†	121	1,194	5,648	64,369	1.17 (0.97-1.41)	1.12 (0.92-1.38)
Simvastatin vs Atorvastatin (ref)						
Overall	2,456 (1.5)	957 (0.9)	124,546	78,697	1.62 (1.50-1.75)	1.37 (1.23-1.53)
Subgroup analyses						
Male	1,187	397	68,659	38,564	1.68 (1.50-1.88)	1.41 (1.19-1.67)
Female	1,269	560	55,888	40,133	1.63 (1.47-1.80)	1.35 (1.16-1.56)
40-64 years	1,400	536	76,666	45,063	1.53 (1.39-1.69)	1.27 (1.09-1.47)
≥65 years	1,056	421	47,880	33,634	1.77 (1.58-1.98)	1.50 (1.27-1.77)
40 vs 10 mg	2,453	635	124,347	52,414	1.62 (1.48-1.76)	1.37 (1.22-1.54)
80 vs 20 mg	X	322	200	26,283	1.24 (0.40-3.88)	1.28 (0.41-4.05)
Sensitivity analyses						
No muscle complaints before CED	2,019	779	112,531	71,549	1.65 (1.52-1.79)	1.35 (1.20-1.53)
No use of CYP3A4 inhibiting drugs*	1,839	715	93,640	57,881	1.59 (1.46-1.73)	1.29 (1.13-1.46)
Additional analyses						
Censoring if dosage change	2,388	894	119,819	73,121	1.64 (1.52-1.77)	1.40 (1.24-1.57)
Broader outcome definition†	3,611	1,270	124,546	78,697	1.79 (1.68-1.91)	1.38 (1.25-1.51)

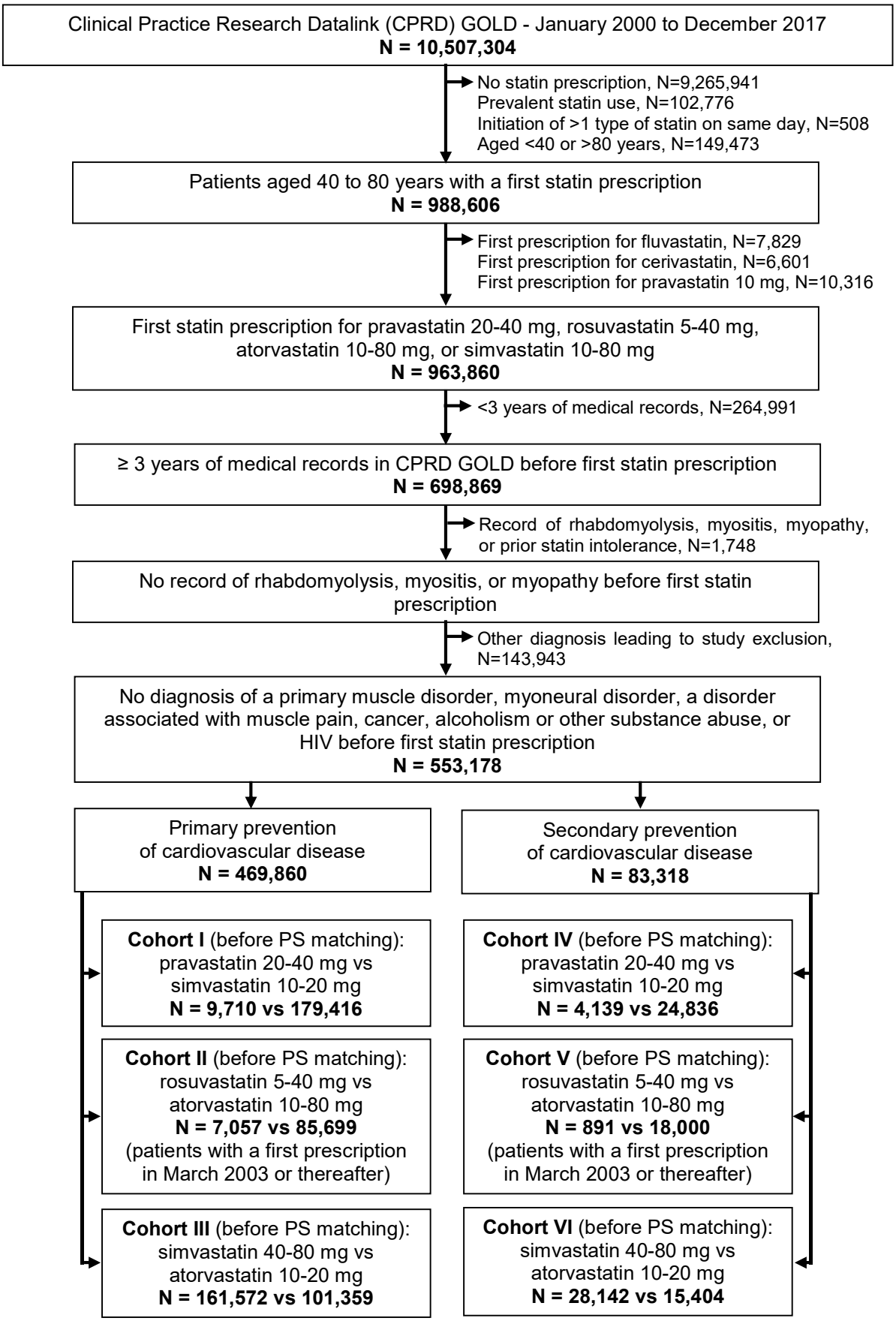
HR hazard ratio; *CI* confidence interval; *Ref* reference; *CYP3A4* Cytochrome P450 3A4; *X* cell contains <5 patients (not shown owing to ethics regulations to preserve confidentiality)

* The analysis was restricted to patients with no prescription for azole antifungals, macrolide antibiotics, cimetidine, cyclosporine, nefazodone, amiodarone, amlodipine, diltiazem, and verapamil within 180 days before the cohort entry date. We censored patients on the day of a first prescription for one of the drugs during follow-up.
† Any recorded Read code for 'statin intolerance' qualified as an outcome of interest.

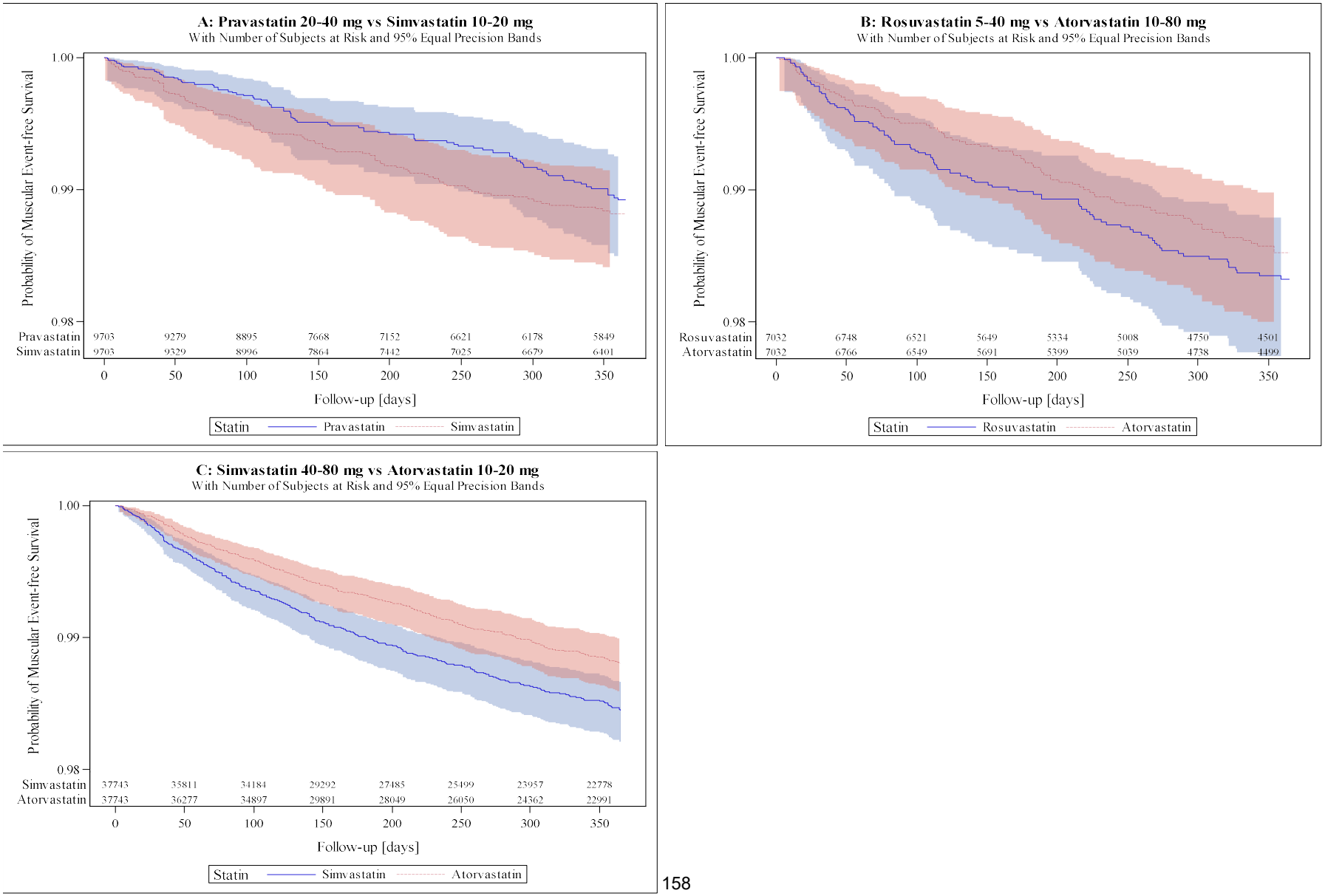
Appendix Table 12. Hazard ratios for muscular events in the secondary prevention cohorts before propensity score matching, using multivariable logistic regression models, and after propensity score matching

	Cohort before propensity score matching						Cohort after propensity score matching				
	Number of events		Total person-years of follow-up		HR (95% CI)		Number of events		Total person-years of follow-up		HR (95% CI)
	Exposed	Comparator	Exposed	Comparator	Crude	Adjusted	Exposed	Comparator	Exposed	Comparator	
Low-intensity statin therapy											
Pravastatin vs Simvastatin (ref)											
Overall	43	276	3,435	20,535	0.93 (0.68-1.29)	1.09 (0.78-1.52)	43	42	3,420	3,474	1.04 (0.68-1.59)
Additional analysis											
Broader outcome definition*	50	463	3,435	20,535	0.65 (0.48-0.87)	0.94 (0.69-1.26)	50	57	3,420	3,474	0.89 (0.61-1.30)
Moderate- to high-intensity statin therapy											
Rosuvastatin vs Atorvastatin (ref)											
Overall	14	259	732	14,658	1.08 (0.63-1.85)	1.23 (0.68-2.23)	13	14	687	698	0.93 (0.44-1.99)
Additional analysis											
Broader outcome definition*	19	339	732	14,658	1.12 (0.71-1.78)	1.19 (0.71-1.98)	18	16	687	698	1.13 (0.58-2.22)
Simvastatin vs Atorvastatin (ref)											
Overall	467	145	23,145	12,864	1.79 (1.48-2.15)	1.39 (1.07-1.80)	95	66	5,633	5,557	1.43 (1.04-1.95)
Additional analysis											
Broader outcome definition*	673	205	23,145	12,864	1.82 (1.56-2.13)	1.31 (1.06-1.62)	142	109	5,633	5'557	1.29 (1.01-1.66)

HR hazard ratio; *CI* confidence interval; *Ref* reference
* Any recorded Read code for 'statin intolerance' qualified as an outcome of interest.



Appendix Figure 1. Flow chart of the selection of the study population



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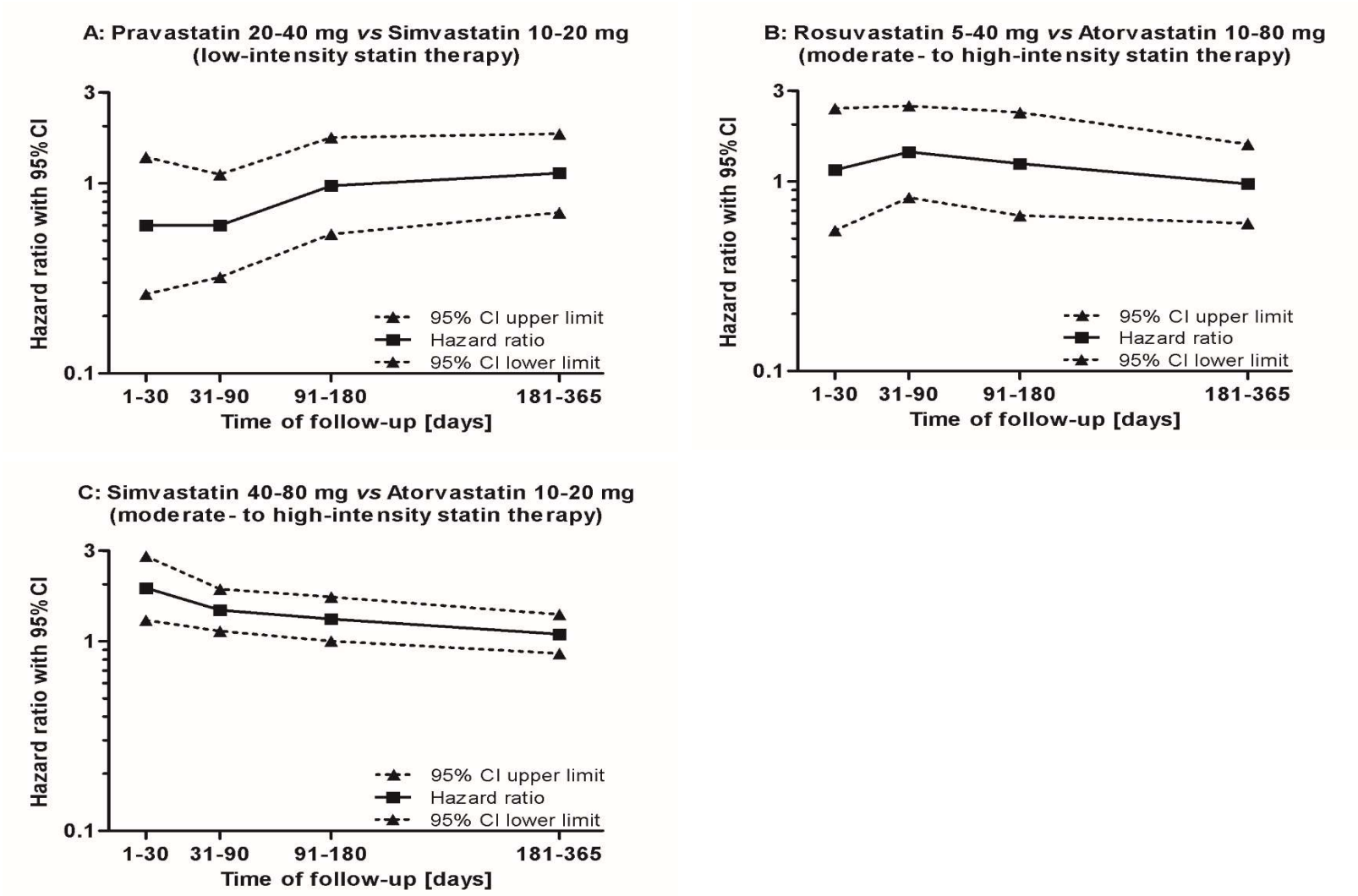
Appendix Figure 2. Kaplan Meier curves for muscular event-free survival after statin initiation in the primary prevention cohorts after propensity score matching



Appendix Figure 3. Hazard ratios for muscular events over time in the primary prevention cohorts after propensity score matching

Chapter 6

References

6 References

1. Mostafa ME, Erbarut-Seven I, Pehlivanoglu B, Adsay V. Pathologic classification of “pancreatic cancers”: current concepts and challenges. *Chin Clin Oncol*. 2017;6(6):59.
2. Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World J Gastroenterol*. 2014;20(32):11182-11198.
3. Diaz KE, Lucas AL. Familial Pancreatic Ductal Adenocarcinoma. *Am J Pathol*. 2019;189(1):36-43.
4. Gheorghe G, Bungau S, Ilie M, et al. Early Diagnosis of Pancreatic Cancer: The key for Survival. *Diagnostics (Basel)*. 2020;10(11):869.
5. Welinsky S, Lucas AL. Familial pancreatic cancer and the future of directed screening. *Gut Liver*. 2017;11(6):761-770.
6. Arnold M, Abnet CC, Neale RE, et al. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology*. 2020;159(1):335-349.e15.
7. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.
8. GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2019;4(12):934-947.
9. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nat Rev Gastroenterol Hepatol*. 2021;18(7):493-502.
10. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30.
11. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. 2021;4(4):e214708.
12. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.
13. National Cancer Institute. Cancer Query System: SEER Survival Statistics. https://seer.cancer.gov/canques/survival.html. Accessed January 11, 2022.

14. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol*. 2019;20(11):1493-1505.

15. Pereira SP, Oldfield L, Ney A, et al. Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2020;5(7):698-710.

16. Hur C, Tramontano AC, Dowling EC, et al. Early Pancreatic Ductal Adenocarcinoma Survival Is Dependent on Size : Positive Implications for Future Targeted Screening. *Pancreas*. 2016;45(7):1062-1066.

17. Chari ST, Kelly K, Hollingsworth MA, et al. Early detection of sporadic pancreatic cancer: summative review. *Pancreas*. 2015;44(5):693-712.

18. Khorana AA, Mangu PB, Katz MHG. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update Summary. *J Oncol Pract*. 2017;13(6):388-391.

19. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology*. 2008;134(1):95-101.

20. Stapley S, Peters TJ, Neal RD, Rose PW, Walter FM, Hamilton W. The risk of pancreatic cancer in symptomatic patients in primary care: a large case–control study using electronic records. *Br J Cancer*. 2012;106(12):1940-1944.

21. Wilson JM, Jungner G. *Principles and Practice of Screening for Disease*. Geneva: World Health Organization; 1968.

22. *Screening Programmes: A Short Guide. Increase Effectiveness, Maximize Benefits and Minimize Harm.* Copenhagen: WHO Regional Office for Europe; 2020.

23. *Population Based Screening Framework*. Canberra: Commonwealth of Australia (Department of Health); 2018.

24. Sullivan L, Boston University School of Public Health. Evaluating Screening Tests. https://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704_probability/bs704_probability4.html. Accessed February 1, 2021.

25. Ruf M, Morgan O. Diagnosis and Screening (Public Health Textbook). https://www.healthknowledge.org.uk/public-health-textbook/disease-causation-diagnostic/2c-diagnosis-screening. Published 2008. Accessed February 1, 2021.

26. Zwahlen M, Low N, Borisch B, et al. Population based screening - The difficulty of how to do more good than harm and how to achieve it. *Swiss Med Wkly*. 2010;140:w13061.

27. Adhikari S. Differences between Screening and Surveillance. https://www.publichealthnotes.com/440-2/. Published 2018. Accessed February 1, 2021.

28. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020;69(1):7-17.

29. Aslanian HR, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. *Gastroenterology*. 2020;159(1):358-362.

30. Blackford AL, Canto MI, Klein AP, Hruban RH, Goggins M. Recent Trends in the Incidence and Survival of Stage 1A Pancreatic Cancer: A Surveillance, Epidemiology, and End Results Analysis. *J Natl Cancer Inst*. 2020;112(11):1162-1169.

31. Keihanian T, Barkin JA, Souto EO. Early detection of pancreatic cancer: risk factors and the current state of screening modalities. *Gastroenterol Heptaol (NY)*. 2021;17(6):254-262.

32. Singhi AD, Maitra A. The Molecular Pathology of Precursor Lesions of Pancreatic Cancer. In: *Pancreatic Cancer*. 2nd edit. New York: Springer-Verlag; 2018:148-176.

33. Bender E. The pancreas problem. *Nat Outlook*. 2020;579(S12).

34. Kenner B, Chari ST, Kelsen D, et al. Artificial Intelligence and Early Detection of Pancreatic Cancer: 2020 Summative Review. *Pancreas*. 2021;50(3):251-279.

35. Lambert A, Schwarz L, Borbath I, et al. An update on treatment options for pancreatic adenocarcinoma. *Ther Adv Med Oncol*. 2019;11:1758835919875568.

36. Johns Hopkins Medicine. Pancreatic Cancer - Whipple Procedure. https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/whipple-procedure. Accessed January 3, 2022.

37. US Preventive Services Task Force, Owens DK, Davidson KW, et al. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. *JAMA*. 2019;322(5):438-444.

38. Poruk KE, Firpo MA, Mulvihill SJ. Screening for pancreatic cancer. *Adv Surg*. 2014;48(1):115-136.

39. Hruban RH, Gaida MM, Thompson E, et al. Why is pancreatic cancer so deadly? The pathologist's view. *J Pathol*. 2019;248(2):131-141.

40. Kenner BJ, Chari ST, Maitra A, et al. Early Detection of Pancreatic Cancer—a Defined Future Using Lessons From Other Cancers: A White Paper. *Pancreas*. 2016;45(8):1073-1079.

41. Canto MI, Harinck F, Hruban RH, et al. International cancer of the pancreas screening (CAPS) consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-347.

42. Copur MS, Talmon GA, Wedel W, Hart JD, Merani S, Vargasi LM. Hereditary vs Familial Pancreatic Cancer: Associated Genetic Syndromes and Clinical Perspective. *Oncol (Williston Park)*. 2020;34(6):196-201.

43. Ayoub F, Davis AM, Chapman CG. Pancreatic Cysts-An Overview and Summary of Society Guidelines. *JAMA*. 2021;325(4):391-392.

44. Tanaka M, Fernández-del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5):738-753.

45. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. *Am J Gastroenterol*. 2018;113(4):464-479.

46. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology*. 2005;129(2):504-511.

47. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol*. 2013;10(7):423-433.

48. Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2016;1(3):226-237.

49. Korc M. Pancreatic cancer-associated diabetes is an “exosomopathy.” *Clin Cancer Res*. 2015;21(7):1508-1510.

50. Ben Q, Cai Q, Li Z, et al. The relationship between new-onset diabetes mellitus and pancreatic cancer risk: A case-control study. *Eur J Cancer*. 2011;47(2):248-254.

51. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnqvist HJ, Larsson J. Pancreatic cancer is associated with impaired glucose metabolism. *Eur J Surg*. 1993;159(2):101-107.

52. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas*. 2013;42(2):198-201.

53. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology*. 2008;134(4):981-987.

54. Tsuchiya R, Noda T, Harada N, et al. Collective review of small carcinomas of the pancreas. *Ann Surg*. 1986;203(1):77-81.

55. Takikawa T, Kikuta K, Kume K, et al. New-Onset or Exacerbation of Diabetes Mellitus is a Clue to the Early Diagnosis of Pancreatic Cancer. *Tohoku J Exp Med*. 2020;252(4):353-364.

56. Alsamarrai A, Das SL, Windsor JA, Petrov MS. Factors that affect risk for pancreatic disease in the general population: a systematic review and meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol*. 2014;12(10):1635-1644.e5.

57. Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. *Ann Surg Oncol*. 2014;21(7):2453-2462.

58. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol*. 2012;23(11):2964-2970.

59. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.

60. Strom BL, Kimmel SE, Hennessy S. Electronic Health Record Databases. In: *Pharmacoepidemiology*. Sixth edit. Hoboken, NJ: Wiley-Blackwell; 2020:241-289.

61. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol*. 2019;48(6):1740-1740g.

62. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69(1):4-14.

63. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet*. 1997;350(9084):1097-1099.

64. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: A systematic review. *Br J Gen Pract*. 2010;60(572):e128-e136.

65. Clinical Practice Research Datalink. CPRD bibliography. https://cprd.com/bibliography. Accessed January 5, 2022.

66. Hart PA, Kamada P, Rabe KG, et al. Weight loss precedes cancer-specific symptoms in pancreatic cancer-associated diabetes mellitus. *Pancreas*. 2011;40(5):768-772.

67. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet*. 2009;373(9682):2215-2221.

68. Pannala R, Leibson CL, Rabe KG, et al. Temporal association of changes in fasting blood glucose and body mass index with diagnosis of pancreatic cancer. *Am J Gastroenterol*. 2009;104(9):2318-2325.

69. Mizuno S, Nakai Y, Isayama H, et al. Risk factors and early signs of pancreatic cancer in diabetes: Screening strategy based on diabetes onset age. *J Gastroenterol*. 2013;48(2):238-246.

70. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921.

71. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67(3):177-193.

72. American Cancer Society. *Breast Cancer Facts & Figures 2017-2018*. Atlanta: American Cancer Society, Inc.; 2017.

73. American Cancer Society. *Colorectal Cancer Facts & Figures 2017-2019*. Atlanta: American Cancer Society; 2017.

74. Kenner BJ, Chari ST, Cleeter DF, Go VL. Early detection of sporadic pancreatic cancer: strategic map for innovation-a white paper. *Pancreas*. 2015;44(5):686-692.

75. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol*. 2009;10(1):88-95.

76. Chari ST. Detecting early pancreatic cancer: problems and prospects. *Semin Oncol*. 2007;34(4):284-294.

77. Olson SH, Xu Y, Herzog K, et al. Weight Loss, Diabetes, Fatigue, and Depression Preceding Pancreatic Cancer. *Pancreas*. 2016;45(7):986-991.

78. Li D, Mao Y, Chang P, et al. Impacts of new-onset and long-term diabetes on clinical outcome of pancreatic cancer. *Am J Cancer Res*. 2015;5(10):3260-3269.

79. Sharma A, Kandlakunta H, Nagpal SJS, et al. Model to Determine Risk of Pancreatic Cancer in Patients with New-Onset Diabetes. *Gastroenterology*. 2018;155(3):730-

739.e3.

80. EUPancreas. Pancreatic Cancer Awareness - Cancer Topics: Risk Factors. http://eupancreas.com/risk-factors. Accessed December 11, 2017.

81. Brodovicz KG, Kou TD, Alexander CM, et al. Impact of diabetes duration and chronic pancreatitis on the association between type 2 diabetes and pancreatic cancer risk. *Diabetes Obes Metab*. 2012;14(12):1123-1128.

82. Bradley MC, Murray LJ, Cantwell MM, Hughes CM. Proton pump inhibitors and histamine-2-receptor antagonists and pancreatic cancer risk: a nested case-control study. *Br J Cancer*. 2012;106(1):233-239.

83. Watson L, Wilson BP, Alsop J, Kumar S. Weight and glycaemic control in type 2 diabetes: what is the outcome of insulin initiation? *Diabetes Obes Metab*. 2011;13(9):823-831.

84. Wilding J, Godec T, Khunti K, et al. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type 2 diabetes: results from the United Kingdom Clinical Practice Research Datalink. *BMC Med*. 2018;16(1):116.

85. Ehrenstein V, Hernandez RK, Ulrichsen SP, et al. Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010. *BMJ Open*. 2013;3(9):e003424.

86. Mueller AM, Meier CR, Jick SS, Schneider C. The potential of glycemic control and body weight change as early markers for pancreatic cancer in patients with long-standing diabetes mellitus: a case-control study. *Pancreas*. 2018;47(7):807-815.

87. Wang F, Gupta S, Holly EA. Diabetes Mellitus and Pancreatic Cancer in a Population-Based Case-Control Study in the San Francisco Bay Area, California. *Cancer Epidemiol Biomarkers Prev*. 2006;15(8):1458-1463.

88. Shields BM, Peters JL, Cooper C, et al. Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. *BMJ Open*. 2015;5(11):e009088.

89. McGovern AP, Fieldhouse H, Tippu Z, Jones S, Munro N, de Lusignan S. Glucose test provenance recording in UK primary care: was that fasted or random? *Diabet Med*. 2017;34(1):93-98.

90. Carpenter JR, Kenward MG. Using observed data to inform assumptions about the missingness mechanism and implications of missing data mechanisms for regression

analyses. In: *Multiple Imputation and Its Application*. 1st edit. Chichester: John Wiley & Sons, Ltd; 2013:21-35.

91. Bartlett JW, Harel O, Carpenter JR. Asymptotically Unbiased Estimation of Exposure Odds Ratios in Complete Records Logistic Regression. *Am J Epidemiol*. 2015;182(8):730-736.

92. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26 Suppl 5:v56-v68.

93. National Institute for Health and Care Excellence. Suspected cancer recognition and referral. https://pathways.nice.org.uk/. Accessed October 15, 2018.

94. Boursi B, Finkelman B, Giantonio BJ, et al. A Clinical Prediction Model to Assess Risk for Pancreatic Cancer Among Patients With New-Onset Diabetes. *Gastroenterology*. 2017;152(4):840-850.e3.

95. Maitra A, Sharma A, Brand RE, et al. A Prospective Study to Establish a New-Onset Diabetes Cohort: From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas*. 2018;47(10):1244-1248.

96. Immunovia. IMMRAY™ PANCAN-D: Prospective studies and next steps - PanDIA-1. https://immunovia.com. Accessed February 4, 2019.

97. National Cancer Institute. SEER Cancer Stat Facts: Pancreatic Cancer. http://seer.cancer.gov/statfacts/html/pancreas.html. Accessed May 23, 2017.

98. Sadr-Azodi O, Gudbjörnsdottir S, Ljung R. Pattern of increasing HbA1c levels in patients with diabetes mellitus before clinical detection of pancreatic cancer – a population-based nationwide case-control study. *Acta Oncol*. 2015;54(7):986-992.

99. Farmer AJ, Rodgers LR, Lonergan M, et al. Adherence to Oral Glucose–Lowering Therapies and Associations With 1-Year HbA1c : A Retrospective Cohort Analysis in a Large Primary Care Database. *Diabetes Care*. 2016;39(2):258-263.

100. Watson L, Das R, Farquhar R, Langerman H, Barnett AH. Consequences of delaying treatment intensification in type 2 diabetes: evidence from a UK database. *Curr Med Res Opin*. 2016;32(9):1465-1475.

101. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. *Int J Obes (Lond)*. 2006;30(3):391-399.

102. Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control

Consortium. *Ann Oncol*. 2014;25(10):2065-2072.

103. Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. Diabetes and risk of pancreatic cancer : a pooled analysis of three large case-control studies. *Cancer Causes Control*. 2011;22(2):189-197.

104. Hart PA, Chari ST. Diabetes mellitus as a result of pancreatic cancer. 2015. https://www.pancreapedia.org/reviews/diabetes-mellitus-as-result-of-pancreatic-cancer. Accessed March 15, 2018.

105. Girelli CM, Reguzzoni G, Limido E, Savastano A, Rocca F. Pancreatic carcinoma: differences between patients with or without diabetes mellitus. *Recenti Prog Med*. 1995;86(4):143-146.

106. Li D, Mao Y. Diabetes as a Risk Factor of Pancreatic Cancer. 2015. https://www.pancreapedia.org/reviews/diabetes-as-risk-factor-of-pancreatic-cancer. Accessed March 15, 2018.

107. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513-1530.

108. National Cancer Institute, Surveillance Research Program. SEER*Explorer: An interactive website for SEER cancer statistics. https://seer.cancer.gov/explorer/. Accessed February 11, 2021.

109. Singhi AD, Koay EJ, Chari ST, Maitra A. Early detection of pancreatic cancer: Opportunities and challenges. *Gastroenterology*. 2019;156(7):2024-2040.

110. Mayo Clinic. Patient Care & Health Information - Diseases & Conditions: Pancreatic cancer. https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/symptoms-causes/syc-20355421. Accessed February 11, 2021.

111. Pelaez-Luna M, Takahashi N, Fletcher JG, Chari ST. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. *Am J Gastroenterol*. 2007;102(10):2157-2163.

112. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. *J Epidemiol Glob Health*. 2020;10(1):107-111.

113. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. *Diabetes Care*. 2009;32 Suppl 2(Suppl 2):S151-S156.

114. Ghosh RE, Crellin E, Beatty S, Donegan K, Myles P, Williams R. How Clinical Practice Research Datalink data are used to support pharmacovigilance. *Ther Adv Drug Saf*. 2019;10:2042098619854010.

115. Huang BZ, Pandol SJ, Jeon CY, et al. New-Onset Diabetes, Longitudinal Trends in Metabolic Markers, and Risk of Pancreatic Cancer in a Heterogeneous Population. *Clin Gastroenterol Hepatol*. 2020;18(8):1812-1821.e7.

116. Cancer Research UK. Pancreatic cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer. Accessed October 10, 2021.

117. Diabetes UK. Diabetes diagnoses double in the last 15 years. Available at: https://www.diabetes.org.uk/about_us/news/diabetes-diagnoses-doubled-prevalence-2021. Accessed October 10, 2021.

118. Frič P, Šedo A, Škrha J, et al. Early detection of sporadic pancreatic cancer: Time for change. *Eur J Gastroenterol Hepatol*. 2017;29(8):885-891.

119. National Institute for Health and Care Excellence. NICE guideline NG28 - Type 2 diabetes in adults: management (published 2015, updated 2020). https://www.nice.org.uk/guidance/ng28. Accessed February 11, 2021.

120. Mueller AM, Meier CR, Jick SS, Schneider C. Weight change and blood glucose concentration as markers for pancreatic cancer in subjects with new-onset diabetes mellitus: A matched case-control study. *Pancreatology*. 2019;19(4):578-586.

121. Wu BU, Butler RK, Lustigova E, Lawrence JM, Chen W. Association of Glycated Hemoglobin Levels with Risk of Pancreatic Cancer. *JAMA Netw Open*. 2020;3(6):e204945.

122. Yuan C, Babic A, Khalaf N, et al. Diabetes, Weight Change, and Pancreatic Cancer Risk. *JAMA Oncol*. 2020;6(10):e202948.

123. Sah RP, Sharma A, Nagpal S, et al. Phases of Metabolic and Soft Tissue Changes in Months Preceding a Diagnosis of Pancreatic Ductal Adenocarcinoma. *Gastroenterology*. 2019;156(6):1742-1752.

124. Baecker A, Kim S, Risch HA, et al. Do changes in health reveal the possibility of undiagnosed pancreatic cancer? Development of a risk-prediction model based on healthcare claims data. *PLoS One*. 2019;14(6):e0218580.

125. U.S. National Library of Medicine. ClinicalTrials.gov: Early Detection Initiative for Pancreatic Cancer (EDI). https://clinicaltrials.gov/ct2/show/NCT04662879. Accessed

December 23, 2021.

126. Duan X, Wang W, Pan Q, Guo L. Type 2 Diabetes Mellitus Intersects With Pancreatic Cancer Diagnosis and Development. *Front Oncol*. 2021;11:730038.

127. Cui Y, Andersen DK. Diabetes and pancreatic cancer. *Endocr Relat Cancer*. 2012;19(5):F9-F26.

128. Li D. Diabetes and pancreatic cancer. *Mol Carcinog*. 2012;51(1):64-74.

129. Wang F, Herrington M, Larsson J, Permert J. The relationship between diabetes and pancreatic cancer. *Mol Cancer*. 2003;2:4.

130. Eibl G, Cruz-Monserrate Z, Korc M, et al. Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer. *J Acad Nutr Diet*. 2018;118(4):555-567.

131. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. *Diabetologia*. 2012;55(4):948-958.

132. Singhi AD, Koay EJ, Chari ST. Early detection of pancreatic cancer. *Gastroenterology*. 2019;156(7):2024-2040.

133. Cummings SR, Browner WS, Hulley SB. Conceiving the Research Question and Developing the Study Plan. In: *Designing Clinical Research*. Fourth Edit. Philadelphia: Lippincott Williams & Wilkins; 2013:14-22.

134. Diabetes UK. *Diabetes: Facts and Stats, Version 4*; 2015. https://mrc.ukri.org/documents/pdf/diabetes-uk-facts-and-stats-june-2015/.

135. Diabetes UK. Number of people with diabetes reaches 4.8 million. https://www.diabetes.org.uk/about_us/news/diabetes-prevalence-2019. Accessed December 18, 2021.

136. U.S. National Library of Medicine. ClinicalTrials.gov: A Study to Establish a New Onset Hyperglycemia and Diabetes Cohort (NOD). https://clinicaltrials.gov/ct2/show/NCT03731637. Accessed December 23, 2021.

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