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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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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.

Introduction

Pancreatic cancer recently surpassed breast cancer to become the third leading cause of cancer-related death in the United States [1]. It is projected to replace colorectal cancer as the second most common cause of cancer-related death by 2030 [2]. 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% [1], the number of new colorectal cancer cases has markedly dropped [1], and survival for both colorectal cancer [3] and breast cancer [4] 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 [4,5].

Experts agree that targeted screening will also play a key role in reducing the number of deaths from pancreatic cancer [6]. 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

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[7]. Surgery, however, is imperative for a favorable prognosis [8]. Pancreatic cancer screening could advance time of diagnosis, leading to the detection of tumors that are still potentially surgically resectable [8]. Given that pancreatic cancer is relatively rare, screening examinations should be limited to subjects at high risk for pancreatic cancer [9]. Today, new onset of diabetes mellitus (DM) after age 50 years is an established marker for non-inherited pancreatic cancer [10]. 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 [11]. 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 [10].

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 [12,13]. 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 [14]. A recent study by Sharma et al. reported that 22% of pancreatic cancer patients studied had lost 2.0–3.9 kg at DM onset, 13% had weight loss of 4.0–5.9 kg, and an additional 36% had already lost 6.0 kg or more by the time of DM onset [15]. 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 [16], 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 [17]. 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 [18].

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.

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 [19]. Validation of diagnostic data recording in the CPRD (using 'Read codes') has demonstrated high accuracy and comprehensiveness [19–21]. The CPRD has been used for numerous observational studies, including studies of pancreatic cancer [22–24] and body weight [25,26] or blood glucose levels [27]. 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 35–89 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 [28], 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 [29] (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 [30]). 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 [31]) 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 one year) and from baseline to the index date (i.e., last weight record before the index date, within one year). Based on the existing literature [12], 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%–9.9%, 10.0%–14.9%, and 15.0% or greater.

Blood glucose levels

Using the approach described previously [28], 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 mmolL/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 [32,33], 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/m^2, 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.

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 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 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%–9.9%, 10.0%–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%–9.9% (1.33 [95% CI 0.86–2.06]) and 10.0%–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 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). In the >2–3 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 >5–6 years before the index date. Blood glucose levels of 5.2–5.6 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). For blood glucose levels of 5.7–6.2 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

Table 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/m^2			
<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.

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 4 provides subject characteristics by type of weight change at DM onset. Cases and controls with weight loss of 3.1%–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 5 shows subject characteristics by *pattern* of blood glucose levels.

Discussion

In this case-control study, relative weight loss as well as normal blood glucose levels (and thus rapid development of

Table 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
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	>5–6 years	>4–5 years	>3–4 years	>2–3 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.

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 [14]. 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%) [14]. 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 [15]. 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%–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 [34]. 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%–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 [7]. Given that

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

Type of weight change at diabetes onset	Cases (N = 588)					Controls (N = 5486)				
	Missing [N = 297]	Weight gain [N = 60]	Stable weight [N = 91]	Weight loss of 3.1%–9.9% [N = 71]	Weight loss of ≥10.0% [N = 69]	Missing [N = 2735]	Weight gain [N = 1082]	Stable weight [N = 989]	Weight loss of 3.1%–9.9% [N = 495]	Weight loss of ≥10.0% [N = 185]
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 visits/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/m^2	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 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/m^2	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.

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%–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 [35], 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 [35].

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 [35] where glucose levels rise abruptly [16]. Type 2 DM, conversely, usually occurs after many years of increasing blood glucose levels [17]. 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 [14]. 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 [18]. 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 one year before DM onset [15].

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 [18].

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 [36,37]. Whether this missing scenario is given in a study cannot be tested [36]. 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 [38]. 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 [31]. 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 [28].

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 [39]. 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 [15,40] 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 [41,42] will offer the opportunity to perform such future studies on large and very complete datasets.

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.

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