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New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer

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Background: Associations between type 2 diabetes, anti-diabetic medications and pancreatic cancer are controversial. This study aims to clarify such associations with new-onset type 2 diabetes and repeated measurements of glycated haemoglobin (HbA1c) levels.

Methods: A nested case–control study was initiated from the Health Improvement Network (THIN) in UK from 1996 to 2010. Information of pancreatic cancer cases was retrieved electronically from the medical records and manually validated. Control subjects were randomly selected and frequency-matched to the cases on sex, age, and calendar years. Multivariable unconditional logistic regression was performed to estimate odds ratios (OR) and 95% confidence intervals (CI), and adjusted for potential confounders.

Results: Among 1 574 768 person-years of follow-up, 529 pancreatic cancer cases and 5000 controls were identified. Type 2 diabetes, or changed HbA1c levels (rather than HbA1c levels at diabetes diagnosis) in diabetes patients ($\geqslant 4$ mmol mol^{-1} compared with <0 mmol mol^{-1}) were followed by an increased OR of pancreatic cancer (OR, 2.16, 95% CI 1.72–2.72 and OR, 5.06, 95% CI 1.52–16.87, respectively). Among the anti-diabetic medications in diabetes patients, the OR for insulin users was 25.57 (95% CI 11.55–56.60), sulphonylureas 2.22 (95% CI 1.13, 4.40), and metformin users 1.46 (95% CI 0.85–2.52), compared with no use of any anti-diabetic medications.

Conclusions: New-onset type 2 diabetes and, particularly, diabetes with rising HbA1c seem to be independent risk factors for pancreatic cancer. The relation between different anti-diabetic medications and pancreatic cancer seems to vary in strength, with the highest risk among users of insulin.

There is an elevated risk of pancreatic cancer among patients with type 2 diabetes. It is unclear, however, whether it is the diabetes *per se* or its treatment that explains this association (Ben *et al*, 2011; Elena *et al*, 2013; Bosetti *et al*, 2014). Furthermore, diabetes is postulated as a manifestation of pancreatic cancer in some studies, which makes the association even more complex. Further research on incident type 2 diabetes and the risk of subsequently diagnosed pancreatic cancer is therefore necessary.

Several mechanisms have been suggested by which diabetes might promote pancreatic cancer. First, diabetes is typically

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preceded by a long period of insulin resistance with a compensatory hyperinsulinaemia and hyperglycaemia, which may promote carcinogenesis. High circulating levels of insulin, glycated haemoglobin (HbA1c), a form of haemoglobin that reflects the average plasma glucose concentration over prolonged periods of time (8–12 weeks), or C-peptide (a component of proinsulin used as a marker of endogenous insulin production) in diabetic patients might increase pancreatic cancer risk (Stolzenberg-Solomon *et al*, 2005; Michaud *et al*, 2007; Grote *et al*, 2011; Wolpin *et al*, 2013). Second, obesity is a risk factor for both diabetes and pancreatic cancer, which might be in the causal pathway. However, diabetes has not only been associated with obesity-related cancers, for example, breast cancer, hepatocellular carcinoma and endometrial cancer (El-Serag *et al*, 2006; Friberg *et al*, 2007; Boyle *et al*, 2012) but also those that are non-obesity related, for example, lung and gastric cancers (Lee *et al*, 2013; Yoon *et al*, 2013). This indicates an independent role of diabetes in cancer development. Third and lastly, some diabetic medications have been associated with a risk of pancreatic cancer (Singh *et al*, 2013; Wang *et al*, 2014; Kowall *et al*, 2015; Walker *et al*, 2015).

Observational studies of diabetes and anti-diabetic medications in relation to pancreatic cancer probably have been afflicted with time-related bias and confounding by indication (Kowall *et al*, 2015). The aim of the present study was to disentangle the roles of diabetes, HbA1c levels in diabetics, and anti-diabetic medications in relation to pancreatic cancer risk in a prospective cohort with validated data from the Health Improvement Network (THIN) in UK.

MATERIALS AND METHODS

Population and study design. This nested case–control study was based on information from the THIN database in UK, which has been described in detail elsewhere (Sjoberg Bexelius *et al*, 2009; Gonzalez-Perez *et al*, 2010). Briefly, THIN is a UK database with longitudinally collected data from computerised primary care medical records, including diagnostic and prescribing information recorded by general practitioners (GPs) during their routine health care practice. The study cohorts were identified from 1 January 1996 through 31 December 2006, and followed up until 31 December 2010. The flow chart of study design is shown in Figure 1. Eligible participants ranged from 20 to 79 years of age. Those with a history of cancer (other than non-melanoma skin cancer) or any pancreatic disease prior to entering the study were excluded. The exclusion was based on READ codes compatible with cancer or pancreatic disease (including any form of pancreatitis and assessment of amylase values) recorded before entering the cohort. Two cohorts, a type 2 newly diagnosed diabetes cohort ($N = 44\,373$) and a non-diabetic general population cohort ($N = 188\,734$), were identified from the source population. Ascertainment of the diabetes cohort is described in greater detail in our previous study (Gonzalez-Perez *et al*, 2010). Briefly, we ascertained all patients within the study base with a READ code of diabetes recorded in the database based on type-specific READ codes (i.e., those that denote explicitly the type of diabetes), the age at diagnosis and the lifetime history of anti-diabetic pharmacological treatment. Among those within the type 2 diabetes cohort, we defined as newly diagnosed diabetes those with the first code compatible with diabetes recorded within the cohort enrolment period. The general population cohort had not only the same eligibility criteria as the type 2 newly diagnosed diabetes cohort but also the additional condition that the individuals had to be free of a recorded diagnosis of diabetes before the start of the study.

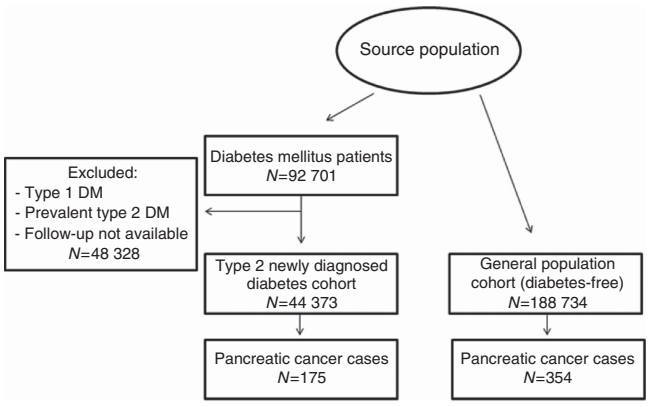

Figure 1. Flow chart of the study design.

Ascertainment of pancreatic cancer cases and controls. All members in the diabetes cohort and the general population cohort were followed up from the date of entry until incident pancreatic cancer, death, or end of the study period (31 December 2010), whichever occurred first. The incident cases of pancreatic cancer were individuals with a first READ code of pancreatic cancer recorded during the follow-up period. To ascertain the pancreatic cancer diagnosis, we manually reviewed the computerised patient profiles (TSB, LM, YL and LGR) after incorporating data from free-text comments, that is, medical notes from the GP's (comments either originate directly from the GP or contain information received from secondary/tertiary care). The initial number of potential pancreatic cancer cases was 544 (179 cases in the type 2 diabetes cohort and 365 in the general population cohort). After exclusion of unconfirmed or prevalent cases (four from the type 2 diabetes cohort and 11 from the general population cohort), 529 patients were retained as incident pancreatic cancer cases for final analysis. Their date of diagnosis was used as the index date.

Incidence density sampling of controls was performed by generating a random date within the study period for each individual among the two study cohorts in whom pancreatic cancer cases were ascertained. If the random date fell within the study member's follow-up contribution time, this person was marked as an eligible control and the random date was used as the index date. A group of 5000 control subjects was randomly selected from the list of eligible controls and frequency-matched to the case subjects on sex, age (± 1 year) and the calendar year.

Identification and categorisation of HbA1c levels. Repeated measurements of HbA1c were retrieved from the medical records for all diabetic patients. We focused on two measurements of HbA1c, one measured closest to the date of the diabetes diagnosis (within 12 weeks after the date of diagnosis of type 2 diabetes) that represents the starting level of HbA1c in diabetic patients, and another measured closest to the date of diagnosis of pancreatic cancer or the index date for controls (within 12 weeks before the index date) that represents the HbA1c level at the time of diagnosis. Because human red blood cells survive for 8–12 weeks (before continuous renewal), HbA1c is used clinically as a reflection of average blood glucose levels over that period of time. HbA1c was categorised into three groups (normal $<42\,\text{mmol mol}^{-1}$, high 42–47 mmol mol^{-1} or very high $\geqslant 48\,\text{mmol mol}^{-1}$) based on UK public health guidelines for the identification of individuals at risk of diabetes (Farmer, 2012). The difference between the two measurements was grouped into <0, 0–4, or $\geqslant 4\,\text{mmol mol}^{-1}$.

Identification and definition of anti-diabetic drug use. The assessment of anti-diabetic drugs included the following four groups: insulin, metformin, sulfonylureas and glitazones. These

medication groups were identified by reviewing medical records. Other anti-diabetic drugs (meglitinides, glucagon-like peptide-1 (GLP-1) and gliptins) were less commonly used by the patients in the current study period and were therefore not included in the analyses. Any of the studied anti-diabetic drug groups were categorised into four patterns of use: non-use (no recorded use between start date and index date), current use (the most recent prescription lasted until the index date or ended within 90 days before it), recent and past use (the most recent prescription ended between 91 and 365 days before the index date and the most recent prescription ended more than 365 days before the index date but occurred after the start date). Duration of current use was further divided into three categories: <1, 1–3 or >3 years. Time from the date of diabetes diagnosis to the index date was grouped into: <1, 1–2, 2.1–5 or >5 years.

Identification of covariates. The following covariates were retrieved from the medical records and considered in the analyses: age; sex; body mass index (BMI); tobacco smoking; alcohol drinking; Townsend deprivation index (a measure of social economic status using five-level score whereby a high value indicates a high level of deprivation); and number of GP visits 1 year before the index date (which was highly related to general comorbidity and used as a proxy for comorbidity).

Statistical analyses. The main analysis was based on a nested case–control design. Using unconditional logistic regression, odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the relative risk of developing pancreatic cancer with regards to the different study exposures, that is, diabetes, time from diabetes diagnosis, HbA1c levels at diabetes diagnosis or before pancreatic cancer diagnosis, increase in HbA1c levels and use of anti-diabetic medications (only use of metformin, only use of sulphonylureas, any use of insulin, combination of oral anti-diabetic medications and no use of any anti-diabetic medication). Two statistical models were employed. The basic model included adjustment for age and sex (calendar year and time from diabetes diagnosis whenever appropriate). In the full model, we further adjusted for tobacco smoking status (categorised into non-smoker, current smoker, former smoker or unknown), alcohol intake (non-user, 1–9, 10–20, 21–41, $\geqslant 42$ units per week or unknown), BMI (<20, 20–24.99, 25–29.99 or $\geqslant 30$), Townsend deprivation index (five categories from least to most deprived, or unknown) and time from diabetes diagnosis when appropriate. Sub-group analyses were performed to assess the risk of pancreatic cancer in diabetic patients.

To reduce selection bias due to sub-clinical pancreatic cancer stages, the first year of follow-up was excluded from the analysis as a sensitivity analysis (results shown in Supplementary Tables). In addition, person-time at risk in each study cohort was classified across strata by age, sex, and calendar year. Age and sex-specific incidence rates of pancreatic cancer were calculated using the corresponding person-years.

All analyses were performed using the SAS Statistical Package (version 9.0, SAS Institute Inc., Gary, NC, USA). All tests were two-sided with a significance level of 0.05. The study was approved by the UK Research Ethics Committee and the Regional Ethical Review Board in Stockholm.

RESULTS

Participants. Overall, 529 incident pancreatic cancer cases occurred in 1 574 768 person-years of follow-up. The incidence of pancreatic cancer was 74.7 per 100 000 person-years in the diabetes cohort and 25.0 per 100 000 person-years in the general population cohort. The average time between first recorded diagnosis of diabetes and occurrence of pancreatic cancer among the 175 cases in the diabetes cohort was 2.46 years (s.d. = 2.50).

Table 1. Basic characteristics of pancreatic cancer cases and controls

	Cases		Controls	
	Number	%	Number	%
Total	529		5000	
Age				
<55	29	5.5	319	6.4
55–65	99	18.7	856	17.1
65–75	210	39.7	1810	36.2
⩾75	191	36.1	2015	40.3
Sex				
Male	307	58.0	2859	57.1
Female	222	42.0	2141	42.9
Calendar year				
1996–1999	45	8.5	401	8.0
2000–2003	123	23.3	1168	23.4
2004–2007	243	45.9	2161	43.2
2008–2010	118	22.3	1270	25.4
GP visits 1 year before index date				
1–3 Times	72	13.6	1094	21.9
4–9 Times	144	27.2	1624	32.5
10+	313	59.2	2282	45.6
Body mass index				
<20	17	3.2	162	3.2
20–24.99	157	29.7	1296	26.0
24.99–29.99	169	31.9	1757	35.1
⩾30	117	22.2	1020	20.4
Missing	69	13.0	765	15.3
Tobacco smoking status				
Non-smoker	199	37.6	2251	45.0
Current smoker	121	22.9	713	14.2
Former smoker	183	34.6	1726	34.5
Unknown	26	4.9	310	6.2
Alcohol use				
Non-user	28	5.3	248	5.0
1–9 Units per week	212	40.1	2100	42.0
10–20 Units per week	73	13.8	640	12.8
21–41 Units per week	31	5.9	284	5.7
42+ Units per week	15	2.8	64	1.3
Unknown	170	32.1	1664	33.2
Townsend deprivation index (quintiles)				
Least deprived	109	20.6	1263	25.3
Deprived2	131	24.8	1164	23.3
Deprived3	116	21.9	1019	20.4
Deprived4	103	19.5	817	16.3
More deprived	51	9.6	548	10.9
Unknown	19	3.6	189	3.8

Some characteristics of cases and controls are presented in Table 1. Age, sex, calendar year and BMI were similarly distributed in cases and controls, while the cases had a higher prevalence of current smokers, increased alcohol consumption, and were more socio-economically deprived (Townsend deprivation index). The cases also had more GP visits in the past year.

Type 2 diabetes and risk of pancreatic cancer. Individuals with newly diagnosed type 2 diabetes were associated with an increased risk of pancreatic cancer (OR 2.16, 95% CI, 1.72, 2.72) compared with non-diabetic individuals (Table 2). The association was strongest during the first year after the diabetes diagnosis (OR 5.30, 95% CI, 2.83, 9.93) when using more than 5 years after diagnosis as the reference category and declined 1–2 years following the diagnosis (OR 3.30, 95% CI, 1.72, 6.23) (Table 2). A sharply decreased incidence rate of pancreatic cancer was observed in the diabetes cohort over time, which was not found in the non-diabetic cohort (Figure 2). The association between diabetes and pancreatic

Table 2. Diabetes, glycated haemoglobin (HbA1c)[a] and risk of pancreatic cancer, expressed as OR with 95% CI

	Cases	Controls	Basic model[b] OR (95% CI)	Full model[c] OR (95% CI)
Diabetes				
No	354	4144	Reference	Reference
Yes	175	856	2.36 (1.94, 2.89)	2.16 (1.72, 2.72)
Among/within diabetes patients				
Time from diabetes diagnosis date to index date				
<1 year	66	170	3.43 (2.06, 5.72)	5.30 (2.83, 9.93)
1–2 years	36	137	2.28 (1.31, 4.00)	3.30 (1.72, 6.33)
2–5 years	48	345	1.20 (0.71, 2.01)	1.45 (0.82, 2.55)
>5 years	25	204	Reference	Reference
HbA1c at diagnosis of diabetes[d]				
Normal (<42 mmol mol^{-1}, or< 6.0%)	14	78	Reference	Reference
High (42–47 mmol mol^{-1}, or 6.0–6.5%)	6	49	0.56 (0.20, 1.57)	0.57 (0.19, 1.70)
Very high (>47 mmol mol^{-1}, >6.5%)	63	280	1.18 (0.62, 2.26)	1.02 (0.51, 2.03)
HbA1c at index date[e]				
Normal (<42 mmol mol^{-1}, or < 6.0%)	15	75	Reference	Reference
High (42–47 mmol mol^{-1}, or 6.0–6.5%)	6	56	0.57 (0.20, 1.57)	0.51 (0.17, 1.54)
Very high (>47 mmol mol^{-1}, or >6.5%)	69	193	1.97 (1.05, 3.71)	1.85 (0.91, 3.73)
Difference between the two HbA1c measurements[f]				
<0 mmol mol^{-1}	17	104	Reference	Reference
0–4 mmol mol^{-1}	27	61	2.55 (1.24, 5.24)	3.22 (1.39, 7.45)
⩾4 mmol mol^{-1}	8	14	3.90 (1.36, 11.19)	5.06 (1.52, 16.87)

Abbreviations: BMI = body mass index; CI = confidence interval; GP = general practitioner; OR = odds ratio.
[a]HbA1c was reported IFCC-recommended units (as mmol mol^{-1}) or DCCT-derived units (as %).
[b]Adjusted for age and sex.
[c]Adjusted for age, sex, BMI (<20, 20–24.99, 25–29.99 or ⩾30), smoking (non-smoker, current smoker, former smoker, or unknown), alcohol drinking (non-user, 1–9 units per week, 10–20 units per week, 21–41 units per week, ⩾42 units per week or unknown), Townsend deprivation index (five categories from least to most deprived, or unknown), calendar year, GP visit 1 year before index date).
[d]HbA1c measured within 12 weeks after diagnosis of diabetes, fully adjusted model includes time since diagnosis of diabetes.
[e]HbA1c measured within 12 weeks before diagnosis of pancreatic cancer or before index date, fully adjusted model includes time since diagnosis of diabetes.
[f]Fully adjusted model includes time since diagnosis of diabetes.

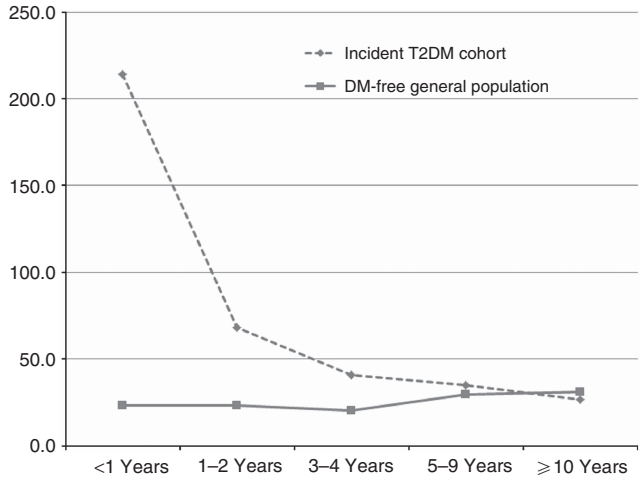

Figure 2. Incidence rate (per 100 000) of pancreatic cancer cases since index date in incident diabetes cohort and diabetes-free general population cohort.

cancer remained two-fold increased after excluding the first year of follow-up (OR 2.04, 95% CI, 1.56, 2.66). Detailed results for the analysis, excluding the first year of follow-up, are available in Supplementary Table 1.

HbA1c and risk of pancreatic cancer. Non-significant associations with pancreatic cancer were found among participants with higher HbA1c levels (⩾48 compared with <42 mmol mol^{-1}) measured close to the diabetes diagnosis (OR 1.02, 95% CI, 0.51, 2.03), and HbA1c measured close to the index date (OR 1.85, 95% CI, 0.91, 3.73) (Table 2). The change of HbA1c between the aforementioned two measurements (the last measurement minus the first measurement with a difference ⩾4 mmol mol^{-1} compared with <0 mmol mol^{-1}) was associated with an increased OR of pancreatic cancer (OR 5.06, 95% CI, 1.52, 16.86) (Table 2).

Anti-diabetic medication and risk of pancreatic cancer. In Table 3, diabetes and use of metformin showed an increased OR compared with non-diabetes and no use of metformin (OR 2.63, 95% CI, 1.99, 3.46). Although for participants who had diabetes and no use of metformin compared with the aforementioned same controls, the quantity of OR seemed to decrease but the difference was not significant. Similar patterns have been observed for sulphonylureas, glitazones and insulin. However, in sulphonylureas or insulin users, diabetes plus relevant medications showed a significantly increased OR compared with diabetes without the relevant medication (for sulphonylureas OR, 3.39, 95% CI, 2.54, 4.54 and 1.56, 95% CI, 1.18, 2.07; for insulin, OR, 10.15, 95% CI, 5.95, 17.32 and 1.85, 95% CI, 1.45, 2.36).

Compared with non-users, ever use (current, recent and past use) of metformin had an increased OR (OR 1.44, 95% CI, 1.01, 2.06; OR 2.05, 95% CI, 1.15, 3.65 for current use, and recent and past use, respectively). This association was similar in other anti-diabetic medications, although results of insulin might be less reliable because of too few cases. In diabetic participants, no significant results were found regarding the association between duration of use of anti-diabetic medications and risk of pancreatic cancer.

Further analyses in the diabetic participants are shown in Table 4. When compared with no use of any anti-diabetic medications, the OR for only use of metformin was 1.46 (95% CI, 0.85, 2.52), sulphonylureas was 2.22 (95% CI, 1.13, 4.40), any use of insulin was 25.57 (95% CI, 11.55, 56.60), combinations of oral anti-diabetic medications (use of two or more oral medications) was 4.84 (95% CI, 2.84, 8.22). Similar results were observed

Table 3. Anti-diabetic medications and risk of pancreatic cancer, expressed as OR with 95% CI

	Cases *n*	Controls *n*	Basic model[a] OR (95% CI)	Full model[b] OR (95% CI)
Metformin				
Non-diabetes, no use of metformin	354	4144	Reference	Reference
*Diabetes, no use of metformin	67	412	1.88 (1.42, 2.50)	1.72 (1.27, 2.33)
Diabetes, use of metformin	108	444	2.82 (2.22, 3.59)	2.63 (1.99, 3.46)
Non-use	421	4556	Reference	Reference
Current use (0–90)	88	383	2.43 (1.88, 3.14)	1.44 (1.01, 2.06)
Recent and past use (90+)	20	61	3.49 (2.09, 5.86)	2.05 (1.15, 3.65)
Current use[c]				
<1 Year	43	137	Reference	Reference
1–3 Years	28	139	0.86 (0.49, 1.53)	0.85 (0.45, 1.59)
⩾3 Years	17	107	1.06 (0.49, 2.29)	0.98 (0.43, 2.26)
Sulphonylureas				
Non-diabetes, no use of sulphonylureas	352	4140	Reference	Reference
Diabetes, no use of sulphonylureas	84	575	1.69 (1.31, 2.19)	1.56 (1.18, 2.07)
Diabetes, use of sulphonylureas	91	281	3.76 (2.89, 4.89)	3.39 (2.54, 4.54)
Non-use	436	4715	Reference	Reference
Current use (0–90)	76	228	3.53 (2.67, 4.67)	2.30 (1.62, 3.26)
Recent and past use (90+)	17	57	3.15 (1.81, 5.47)	2.03 (1.12, 3.68)
Current use[c]				
<1 year	44	79	Reference	Reference
1–3 years	20	77	0.61 (0.31, 1.19)	0.57 (0.26, 1.25)
⩾3 years	10	71	0.42 (0.17, 1.04)	0.42 (0.14, 1.21)
Glitazones				
Non-diabetes, no use of glitazones	354	4144	Reference	Reference
Diabetes, no use of glitazones	143	760	2.18 (1.76, 2.69)	1.99 (1.57, 2.54)
Diabetes, use of glitazones	32	96	3.88 (2.56, 5.90)	3.63 (2.33, 5.68)
Non-use	497	4904	Reference	Reference
Current use (0–90)	24	70	3.30 (2.05, 5.30)	1.88 (1.13, 3.14)
Recent and past use (90+)	8	26	2.95 (1.33,6.55)	1.66 (0.73, 3.78)
Current use[c]				
<1 year	16	37	Reference	Reference
⩾1 years	8	33	1.06 (0.33, 3.49)	7.09 (0.37, 136.96)
Insulin				
Non-diabetes, no use of insulin	354	4143	Reference	Reference
Diabetes, no use of insulin	144	825	2.02 (1.63, 2.50)	1.85 (1.45, 2.36)
Diabetes, use of insulin	31	31	11.59 (6.95, 19.34)	10.15 (5.95, 17.32)
Non-use	498	4968	Reference	Reference
Current use (0–90)	29	31	9.08 (5.42, 15.21)	5.13 (2.97, 8.86)
Recent and past use (90+)	2	1	19.31 (1.74, 214.00)	11.12 (0.95, 130.06)
Current use[c]				
<1 year	19	11	Reference	Reference
⩾1 years	10	20	0.50 (0.12, 2.10)	0.71 (0.02, 33.60)

Abbreviations: CI = confidence interval; GP = general practitioner; OR = odds ratio.

[a]Adjusted for age and sex.

[b]Adjusted for age, sex, body mass index (<20, 20–24.99, 25–29.99, or ⩾30), smoking (non-smoker, current smoker, former smoker or unknown), alcohol drinking (non-user, 1–9, 10–20, 21–41, ⩾42 units per week or unknown), Townsend deprivation index (five categories from least to most deprived, or unknown), calendar year, GP visit 1 year before index date) and diabetes (when appropriate for anti-diabetics).

[c]Analysis within diabetes, adjusted for age, sex, body mass index, smoking, alcohol drinking, Townsend deprivation index, calendar year, GP visit 1 year before index date and time since diagnosis of diabetes.

for diabetes diagnosed within one year. For diabetes diagnosed ⩾1 year, the risk of only use of sulphonylureas became non-significant (OR 1.07, 95% CI, 0.35, 3.27) (Table 4).

DISCUSSION

This study suggests that new-onset diabetes is associated with an increased risk of pancreatic cancer, especially early after the diagnosis, which is a finding supported by the association between elevated HbA1c levels and an increased risk of pancreatic cancer. Anti-diabetic medications showed different associations to the risk of pancreatic cancer, with an increased risk of pancreatic cancer present in insulin users and the least increased risk seen in metformin users.

Previous studies have also found diabetes to be associated with pancreatic cancer (Ben *et al*, 2011; Elena *et al*, 2013). However, the majority of prior epidemiological studies have evaluated long-standing diabetes as a possible causative or inductive factor for subsequent pancreatic cancer (Boyle *et al*, 2012; Bosetti *et al*, 2014), while, in our study, we have instead chosen to focus on new-onset diabetes. Although an analysis excluding the first year following the diabetes diagnosis attenuated the association, a statistically significant association remained. Hyperinsulinaemia and insulin

Table 4. Risk of pancreatic cancer in diabetes patients associated with use of different anti-diabetic medications, expressed as OR with 95% CI

	Cases	Control	OR (95% CI)[a]	OR (95% CI)[b]
All diabetes				
Only use of metformin	30	215	1.44 (0.86, 2.42)	1.46 (0.85, 2.52)
Only use of sulphonylureas	19	85	2.00 (1.08, 3.69)	2.22 (1.13, 4.40)
Any use of insulin	31	31	21.79 (10.71, 44.30)	25.57 (11.55, 56.60)
Use of two or more medications except insulin	56	204	4.65 (2.84, 7.61)	4.84 (2.84, 8.22)
No use of any anti-diabetic medications	39	321	Reference	Reference
Less than 1 year from diagnosis of diabetes				
Only use of metformin	13	44	1.56 (0.70, 3.48)	1.59 (0.66, 3.83)
Only use of sulphonylureas	14	21	3.36 (1.44, 7.86)	3.78 (1.38, 10.35)
Any use of insulin	6	1	29.59 (3.34, 262.46)	31.15 (2.73, 356.13)
Use of two or more medications except insulin	14	11	6.78 (2.61, 17.63)	8.00 (2.73, 23.47)
No use of any anti-diabetic medications	19	93	Reference	Reference
More than 1 year from diagnosis of diabetes				
Only use of metformin	17	171	1.38 (0.69, 2.74)	1.41 (0.68, 2.93)
Only use of sulphonylureas	5	64	0.96 (0.34, 2.71)	1.07 (0.35, 3.27)
Any use of insulin	25	30	16.34 (7.56, 35.29)	18.25 (7.50, 44.41)
Use of two or more medications except insulin	42	193	4.00 (2.18, 7.35)	3.91 (2.00, 7.64)
No use of any anti-diabetic medications	20	228	Reference	Reference

Abbreviations: CI = confidence interval; GP = general practitioner; OR = odds ratio.
[a]Adjusted for age, sex and time since diagnosis of diabetes.
[b]Adjusted for age, sex, time from diagnosis of diabetes, body mass index, calendar year, smoking, alcohol drinking, physical activity, GP visit 1 year before index date and Townsend deprivation index.

resistance may be key factors in the development of pancreatic cancer. Diabetic patients show a progressive metabolic disorder, from pre-diabetes to diabetes and, finally, to the late stages of diabetes with severe comorbidities that could affect the risk of many cancers (Hsueh *et al*, 2010; Tabak *et al*, 2012). Subjects who have had diabetes for many years are more likely to have reached the point of pancreatic exhaustion, which results in a gradually declining insulin production, and therefore might be experiencing a status of hypoinsulinemia. This seemed to be consistent with the negative association between the duration of diabetes and pancreatic cancer in this study. Previous studies were generally based on self-reported diabetes, which might lead to misclassification of the exposed with respect to the hypothesised biological mechanism linking new-onset diabetes and cancer (Flood *et al*, 2010; Onitilo *et al*, 2013).

Furthermore, the present study showed that increasing HbA1c levels, which potentially indicate increased severity of diabetes, was associated with a three-fold or more increased risk of pancreatic cancer compared with diabetic patients with low changes of HbA1c levels after diabetes diagnosis. This result may further corroborate the pivotal role of new-onset diabetes with typical hyperglycaemia in the development of pancreatic cancer. Few studies reported the association between change of HbA1c in diabetes and pancreatic cancer. HbA1c reflects average blood sugar levels over a period of weeks/months. Some studies have demonstrated that improving HbA1c for people with types 1 or 2 diabetes cuts the risk of microvascular complications. Therefore deterioration of HbA1c may increase the risk of diabetes complications, including cancer. Although limited number of existing studies examined the role of elevated HbA1c on pancreatic cancer (Grote *et al*, 2011; Wolpin *et al*, 2013), the increased HbA1c levels indicate poorly controlled diabetes, which, reasonably, contributes to the metabolic derangement that may lead to pancreatic cancer development.

Controversy does exist, however, regarding the role of diabetes in pancreatic cancer as 50–80% of patients with this cancer have concomitant diabetes, which often predates the diagnosis of cancer by 1 to 2 years (Pannala *et al*, 2008). Epidemiological evidence shows that patients with newly diagnosed diabetes have a higher detection rate of pancreatic cancer (Pannala *et al*, 2009), which was indicated in the present study as well. The new-onset diabetes in pancreatic cancer is possibly a paraneoplastic phenomenon caused by tumour-secreted products. This notion was strengthened by recent studies that proposed adrenomedullin, an amino-acid polypeptide, as a strong candidate for a mediator of diabetes in pancreatic cancer (Aggarwal *et al*, 2012; Sah *et al*, 2013). Other studies have supported the assertion that diabetes may be a marker for pancreatic cancer in some individuals (Giovannucci *et al*, 2010). Diabetes associated with pancreatic cancer may result from insulin resistance induced by a paraneoplastic syndrome or pancreatic cancer associated cell dysfunction in insulin production. Animal studies suggest that glucose intolerance may be an early feature of pancreatic cancer (Chari, 2014). Hyperglycaemia induced by pancreatic cancer in human beings can be cured or ameliorated by surgical resection of the pancreatic tumour.

The role of anti-diabetic medication in pancreatic cancer aetiology has been proposed to either increase the risk of cancer (insulin) or ameliorate the risk (metformin) (Evans *et al*, 2005; Bowker *et al*, 2006; Elena *et al*, 2013; Karlstad *et al*, 2013; Wang *et al*, 2014; Kowall *et al*, 2015; Walker *et al*, 2015) but results are inconsistent (Soranna *et al*, 2012; Karlstad *et al*, 2013; Singh *et al*, 2013). Two meta-analyses on metformin and pancreatic cancer showed inconsistent results, which might have been due to different inclusion criteria for the two studies (Singh *et al*, 2013; Wang *et al*, 2014). Furthermore, in a recent randomised clinical trial, addition of a conventional anti-diabetic dose of metformin does not improve outcome in patients with advanced pancreatic cancer treated with gemcitabine and erlotinib (Kordes *et al*, 2015), although significantly negative association of metformin with cancer were showed *in vitro*, *in vivo* studies (Cifarelli *et al*, 2015; Tan *et al*, 2015; Yue *et al*, 2015) or in epidemiological studies (Evans *et al*, 2005). Similar inconsistencies were found in another three meta-analyses on insulin, or sulfonylurea and pancreatic cancer (Soranna *et al*, 2012; Singh *et al*, 2013). In addition, two published randomised clinical trials were underpowered and provided non-significant results with wide, non-informative 95% CIs (Home *et al*, 2010). The considerable heterogeneity between studies, for example, study design, setting or comparator drugs, might explain the different results. Furthermore, confounding by indication and reverse causality cannot be ruled out in almost all of these original studies.

In our study, the positive association of diabetes or anti-diabetic medication use with a risk of pancreatic cancer could not be fully differentiated from each other because of time-related bias and confounding by indication. However, the results based on elevated HbA1c levels seem to further corroborate the role of diabetes itself rather than the use of anti-diabetic medication in the aetiology of pancreatic cancer. Specifically, our study indicates the magnitude of pancreatic cancer risk in different anti-diabetic medications, which ranked from slightly increased to higher ORs for the following medications: metformin, sulphonylurea, a combination of oral anti-diabetic medications, and finally, insulin. One cannot exclude that part of the increased risk among insulin users is due to confounding by indication. However, the magnitude of the association favours an independent role of the medication *per se*, in addition to the severity of disease. The underlying mechanism of the slightly least increased risk in metformin users compared with other diabetic medications has been demonstrated in experimental studies. Metformin may disrupt a crosstalk between insulin receptor and other growth-factor signalling systems in human pancreatic cancer cells (Kisfalvi *et al*, 2009). An interesting piece of new information is that the administration of metformin seems to block mammalian target of rapamycin (mTOR) activity and inhibit the growth of human pancreatic cancer cells in some animal models (Rozengurt, 2014).

Strengths of our study include the population-based cohort study design, validated pancreatic cancer diagnosis, and detailed prospective information on drug exposure and potential confounding factors. The source of the study population, the THIN database, is representative of the UK population and has been validated for use in epidemiological studies (Bourke *et al*, 2004; Lewis *et al*, 2007). The use of administrative register data may, however, result in ascertainment bias with an under appreciation or misclassification of diabetes or pancreatic cancer, although this bias may be minor because the administrative data were validated by the reviewing of medical records. Histological confirmation of coded pancreatic cancer diagnoses was not available, raising the possibility that some pancreatic cancers may have been misclassified, and whether such misclassification could be differential or non-differential cannot be determined. Furthermore, missing data on HbA1c levels may bias the results, although availability of HbA1c was reasonably distributed from the time of diabetes diagnosis. Further studies with completely dynamic information of HbA1c are warranted to verify the current findings. Finally, our study was limited by a lack of dietary history, which may potentially confound the results. As the causality of pancreatic cancer is largely unclear, residual confounding by unknown risk factors may result in chance errors.

In conclusion, these data suggest that new-onset diabetes or elevated HbA1c levels after diabetes confers an increased risk of pancreatic cancer. Specific anti-diabetic medications carry different risks of pancreatic cancer, with a particularly increased risk among insulin users, and gradually less increased risks among users of combination of oral anti-diabetic medications, sulphonylurea and metformin, although these associations warrant further research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yunxia Lu, Luis Alberto García Rodríguez and Tomas S Bexelius: conceptualisation and design; Luis Alberto García Rodríguez: data collection; Linnéa Malgerud: data preparation and review of medical records; Yunxia Lu, Luis Alberto García Rodríguez and Antonio González-Pérez: data analysis; all: reporting of results and interpretation of data; Yunxia Lu: drafting of manuscript; all: contribution to critical comments and revisions, and final approval of the version to be published.

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