

Metformin and the risk of head and neck cancer: a case–control analysis

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Aims: Metformin use has been associated with a decreased risk of some cancers, although data on head and neck cancer (HNC) are scarce. We explored the relation between the use of antidiabetic drugs and the risk of HNC.

Methods: We conducted a case–control analysis in the UK-based Clinical Practice Research Datalink (CPRD) of people with incident HNC between 1995 and 2013 below the age of 90 years. Six controls per case were matched on age, sex, calendar time, general practice and number of years of active history in the CPRD prior to the index date. Other potential confounders including body mass index (BMI), smoking, alcohol consumption and comorbidities were also evaluated. The final analyses were adjusted for BMI, smoking and diabetes mellitus (or diabetes duration in a sensitivity analysis). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Use of metformin was neither associated with a statistically significant altered risk of HNC overall (1–29 prescriptions: adjusted OR 0.87, 95% CI 0.61–1.24 and ≥ 30 prescriptions adjusted OR 0.80, 95% CI 0.53–1.22), nor was long-term use of sulphonylureas (adjusted OR 0.87, 95% CI 0.59–1.30), or any insulin use (adjusted OR 0.92, 95% CI 0.63–1.35). However, we found a (statistically non-significant) decreased risk of laryngeal cancer associated with long-term metformin use (adjusted OR 0.41, 95% CI 0.17–1.03).

Conclusions: In this population-based study, the use of antidiabetic drugs was not associated with a materially altered risk of HNC. Our data suggest a protective effect of long-term metformin use for laryngeal cancer.

Keywords: antidiabetic drug, diabetes mellitus, metformin, observational study, pharmacoepidemiology

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Introduction

Head and neck cancer (HNC) comprises a heterogeneous group of cancers arising in a variety of sites within the head and neck region, including the oral cavity, pharynx (nasopharynx, oropharynx and hypopharynx), larynx, the salivary glands and the nasal cavity and the middle ear [1]. Worldwide more than 500 000 new cases of HNC were diagnosed in 2012 [2]. Smoking and alcohol consumption are well-established risk factors for HNC with their effects being multiplicative [3,4]. Low body weight has been associated with an increased HNC risk [5]. Additionally, a family history with a first-degree relative increases the risk of developing HNC 1.7-fold (95% confidence interval, CI 1.2–2.3) [6,7], and incidence rates of HNC have been shown to vary by ethnic group [8–10]. Furthermore, infections with human papillomavirus (HPV) or Epstein–Barr virus (EBV) have been associated with HNC [11,12].

Findings on the association between diabetes mellitus and HNC have been contradictory: a prospective cohort study from Japan reported an adjusted hazard ratio of 3.61 (95% CI 1.16–11.2) for cancer of the larynx in association with a prior

diabetes diagnosis [13]. In a study from Italy and Switzerland, the risks for cancer of the oral cavity/pharynx [adjusted odds ratio (OR) 1.58, 95% CI 1.15–2.18] as well as for laryngeal cancer (adjusted OR 1.30, 95% CI 0.91–1.85) were also increased in diabetic patients [14]. Data from the USA as well as pooled data from Europe, the USA and Japan provided no evidence for an association between diabetes mellitus and HNC risk [15,16]. Finally, a study in US veterans reported a decreased risk for cancer of the buccal cavity [adjusted relative risk (RR) 0.85, 95% CI 0.82–0.89] as well as for laryngeal cancer (adjusted RR 0.76, 95% CI 0.71–0.80) [17] in association with diabetes.

Exposure to metformin has been associated with reduced risks for some cancer types (e.g. breast cancer, cancer of the pancreas or liver) and for cancer overall but results remain controversial [18,19]. The potential mechanisms by which metformin may exert antiproliferative activities are not fully understood. In addition to decreasing insulin resistance, metformin has been shown to inhibit the mammalian target of rapamycin complex (mTORC) through the activation of AMP-activated protein kinase (AMPK) [20]. By upregulation of AMPK, metformin acts as a direct tumour growth inhibitor [20]. Additionally, metformin appears to decrease mitochondrial endogenous reactive oxygen species (ROS) [21]. The

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resulting decrease in oxidative stress leads to reduced DNA damage and mutagenesis in cells.

In HNC, the mTOR pathway is frequently deregulated [22]. In a mouse model, metformin prevented the development of oral squamous cell carcinomas from carcinogen-induced premalignant lesions [23]. Furthermore, in a recently published *in vitro* observation, metformin suppressed the growth of human head and neck squamous cell carcinoma via global inhibition of protein translation predominantly mediated by AMPK activation [24].

Very little is known on the HNC risk after exposure to other antidiabetics. Three experimental studies investigated the effect of thiazolidinediones on the development of HNC, two of them suggesting a protective effect [25,26] whereas one study did not find any inhibitory effect on cancer growth [27].

So far, no observational studies have reported on the association between metformin or of other antidiabetic drugs, and the risk of HNC. Therefore, the objective of this study was to assess the risk of HNC in users of metformin or other antidiabetic drugs, and to compare them to individuals with no exposure to these drugs.

Materials and Methods

Data Source

We performed a retrospective case–control analysis using data from the Clinical Practice Research Datalink (CPRD, formerly the General Practice Research Database, GPRD) [28]. The CPRD provides health care information on some eight million patients in the UK and has been previously described in detail [29,30]. General practitioners (GPs) record information on demographics, diagnoses and drug prescriptions as well as patient referrals and hospital admissions, using standard coding systems. The GPs generate prescriptions directly using the computer, and this information is automatically transcribed into the individual computerized patient records. Additionally, the CPRD holds information regarding lifestyle variables such as body mass index (BMI), alcohol consumption and smoking. Recorded information on drug exposure and diagnoses has been validated repeatedly and has proven to be of high quality [31–33]. The CPRD currently covers about 7% of the UK population, and enrolled patients are representative of the UK with regard to age, gender and geographic distribution [34]. The CPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators had access to anonymous information only.

Study Population

The study population included all patients in the CPRD below the age of 90 years between January 1995 and July 2013. Cases were all persons in the study population who had an incident diagnosis of HNC recorded during the study period. The date of the HNC diagnosis will subsequently be referred to as the ‘index date’. We excluded all patients with a recorded diagnosis of HIV, alcoholism or any malignancy prior to the index date

as well as those with <3 years of medical history in the CPRD computer records prior to the index date.

From the study population, we identified for each case with HNC at random up to six controls without evidence for HNC. The controls were matched to cases on calendar time (same index date), age, sex, general practice and number of years of active history in the CPRD prior to the index date. The same exclusion criteria were applied to controls as to cases.

After matching, we shifted the index date back by 2 years. This was performed to take into account the cancer latency and to reduce the risk of detecting spurious findings due to possible protopathic bias.

Exposure to Metformin or Other Antidiabetic Agents

We identified, from the computer records, all prescriptions for insulin and for oral antidiabetic drugs (metformin, sulphonylureas, thiazolidinediones, glinides, gliptins, incretins and glucosidase inhibitors) prior to the shifted index date. We classified patients by the type of antidiabetic treatment and defined exposure duration based on the recorded number of prescriptions prior to the index date, classifying them into short-term (1–29 prescriptions) or long-term (≥ 30 prescriptions) users. Glinides, gliptins, glucagon-like peptide-1 agonists and glucosidase inhibitors were not included in the final multivariate model, because exposure to these drugs was too low. We compared the use of antidiabetic drugs to non-use of these substances. As many patients used more than one antidiabetic drug, we adjusted for sequential or concurrent use of various antidiabetic drugs in the multivariate models.

Statistical Analysis

We conducted conditional logistic regression analyses using the SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA) to calculate RR estimates as ORs with 95% CIs. We controlled for age, sex, general practice, calendar time and years of recorded history in the database by matching, and for smoking status (never, ex-smoker, current or unknown), BMI (<25 , $25–29.9$, ≥ 30 kg/m² or unknown) and diagnosed diabetes mellitus in the multivariate model. In addition, we explored the association between various potential confounders and the risk of HNC in univariate analyses including alcohol consumption, recorded HPV or EPV infections, asbestosis, other comorbidities such as congestive heart failure, ischaemic heart disease, stroke, hypertension, dyslipidaemia, as well as drug therapy with acetylsalicylic acid (ASA) or statins. As these variables did not alter the RR estimates for the association between the use of antidiabetic drugs and the risk of HNC by more than 10%, they were not included in the final multivariate analyses. Furthermore, we assessed whether cancer cases had recordings for radiotherapy, chemotherapy, surgery for HNC or specific oncology codes in association with their diagnosis of an HNC to minimize the risk of potential misclassification of diagnosed cancer. We performed a sensitivity analysis restricted to patients with at least one of these codes.

As diabetes mellitus has been shown to be associated with an increased cancer risk in some previous studies, we further assessed the risk of HNC in association with antidiabetic drug

use in a sample of the study population restricted to diabetic patients and controls only. For this sensitivity analysis, we newly matched diabetic HNC cases with diabetic cancer-free controls, and we additionally analysed diabetes duration. Diabetes duration was defined as the time span between the date of a first recorded diagnosis of diabetes and the index date.

Finally, we performed separate analyses for cases with cancer of the oral cavity, the pharynx or the larynx.

Results

We identified a total of 2874 cases with incident HNC and 17 244 matched controls. Almost two-thirds of the cases were men (63.8%). The mean (\pm s.d.) age of cases and controls at the index date was 62.0 (\pm 14.1) years. The mean duration of history recorded in the CPRD before the cancer diagnosis was 10.6 (\pm 4.7) years. A cancer diagnosis of the oral cavity was present in 1206 cases (42%), 570 cases (20%) had pharyngeal cancer and 680 cases (24%) had laryngeal cancer. The remainder either had a diagnosis of cancer of the nasal cavity (73 cases; 2.5%) or the site of cancer was not specified (345 cases; 12%). A record of radiotherapy or chemotherapy, an oncology code, or HNC-related surgery was documented in 84% of the cancer cases after the index date.

Detailed characteristics of cases and controls are displayed in Table 1. There was little information recorded on asbestosis, EBV or HPV infections, so that we were not able to assess the influence of these parameters on the HNC risk. Information on ethnicity was missing in more than half of the cases. The majority (>95%) of the cases with information on ethnicity were Caucasians. The BMI values were missing for 24.6% of cases and for 20.2% of controls. The numbers of missing values for BMI were lower in the analysis restricted to diabetic patients (10.8% in cases and 5.4% in controls), and an analysis omitting patients with missing values for BMI yielded closely similar results with risk estimates within a range of 10%.

The risk of HNC was increased for current smokers compared with non-smokers (crude OR 3.05, 95% CI 2.74–3.39), and for patients with current or past alcohol consumption (see Table 1). Use of ASA and statins was not associated with an altered risk of HNC. A diagnosis of diabetes mellitus was not associated with an increased risk of HNC (crude OR 0.96, 95% CI 0.83–1.12). A long-term history of diabetes (>8 years) yielded a crude OR of 1.00 (95% CI 0.66–1.51) compared to patients who had diabetes for <4 years. A1c levels of patients with a recorded A1c within 1 year before the index date were <48 mmol/l (A1c of 6.5%) in 36.5% of the cases and 48 mmol/l or higher in 63.5% of the cases (unknown or last A1c assessment >1 year before the index date in 27%), but inclusion of A1c information in the multivariate model did not change the results.

Long-term use of metformin (\geq 30 prescriptions) was neither associated with a decreased risk of HNC in the main analysis (adjusted OR 0.80, 95% CI 0.53–1.22) nor in the analysis restricted to diabetic patients (adjusted OR 0.92, 95% CI 0.58–1.45) (Tables 2 and 3). The OR was slightly lower if we restricted the analysis to patients without any insulin use

Table 1. Characteristics of head and neck cancer cases and controls.

	Cases (%) (n = 2874)	Controls (%) (n = 17 244)	Crude OR (95% CI)
Age (years)			
<40	160 (5.6)	900 (5.2)	
40–59	1 011 (35.2)	5 944 (34.5)	—
60–69	771 (26.8)	4 601 (26.7)	—
70–79	652 (22.7)	4 008 (23.2)	—
\geq 80	280 (9.7)	1 791 (10.4)	—
Sex			
Male	1 834 (63.8)	11 004 (63.8)	—
Female	1 040 (36.2)	6 240 (36.2)	—
Smoking			
Non-smoker	835 (29.1)	7 583 (44.0)	1.00 (referent)
Current	973 (33.9)	3 135 (18.2)	3.05 (2.74–3.39)
Past	720 (25.1)	4 704 (27.3)	1.41 (1.26–1.58)
Unknown	346 (12.0)	1 822 (10.6)	1.88 (1.61–2.19)
BMI			
<25	934 (32.5)	5 164 (30.0)	1.00 (referent)
25–29.9	823 (28.6)	5 611 (32.5)	0.80 (0.73–0.89)
\geq 30	409 (14.2)	2 994 (17.4)	0.74 (0.65–0.84)
Unknown	708 (24.6)	3 475 (20.2)	1.21 (1.08–1.37)
Alcohol use			
Never	384 (13.4)	2 582 (15.0)	1.00 (referent)
Current	1 993 (69.4)	11 954 (69.3)	1.13 (1.00–1.28)
Past	59 (2.1)	225 (1.3)	1.79 (1.31–2.43)
Unknown	438 (15.2)	2 483 (14.4)	1.22 (1.03–1.43)
Comorbidities			
CHF	73 (2.5)	405 (2.4)	1.09 (0.84–1.41)
IHD	312 (10.9)	1 928 (11.2)	0.96 (0.84–1.10)
Hypertension	851 (29.6)	5 173 (30.0)	0.98 (0.89–1.07)
Stroke/TIA	164 (5.7)	900 (5.2)	1.10 (0.93–1.31)
Dyslipidaemia	300 (10.4)	1 939 (11.2)	0.91 (0.80–1.04)
Diabetes	216 (7.5)	1 343 (7.8)	0.96 (0.83–1.12)
EBV	10 (0.4)	86 (0.5)	0.69 (0.36–1.34)
Asbestosis	12 (0.4)	46 (0.3)	1.57 (0.83–2.98)
Statins			
No prior use	2 333 (81.2)	13 941 (80.9)	1.00 (referent)
1–14 Rx	210 (7.3)	1 202 (7.0)	1.04 (0.89–1.22)
\geq 15 Rx	331 (11.5)	2 101 (12.2)	0.93 (0.81–1.07)
ASA			
No prior use	2 210 (76.9)	13 383 (77.6)	1.00 (referent)
1–14 Rx	295 (10.3)	1 680 (9.7)	1.07 (0.93–1.23)
\geq 15 Rx	369 (12.8)	2 181 (12.7)	1.03 (0.91–1.18)

ASA, acetylsalicylic acid; BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; EBV, Epstein–Barr virus infection; IHD, ischaemic heart disease; OR, odds ratio; Rx, prescriptions; TIA, transient ischaemic attack.

(long-term metformin use OR 0.68, 95% CI 0.42–1.09). In the sensitivity analysis restricted to the 84% of cases with recorded radiotherapy, chemotherapy, a recorded oncology code, or HNC-related surgery (and their controls), we found an adjusted OR of 0.81 (95% CI 0.52–1.25) for HNC in association with the long-term use of metformin. To address the potential bias of exposure time opportunity (time window bias), we explored whether cases with long-term metformin use (\geq 30 prescriptions) had longer duration of diabetes mellitus than controls and, therefore, had a higher probability to receive a prescription. Among all long-term metformin users, 90% of the cases had a diabetes duration of more than 4 years and 64% of more

Table 2. Odds ratios for head and neck cancer in relation to antidiabetic drug use and number of prescriptions for antidiabetic drugs in all cases and controls.

Drugs and no. of prescriptions	Cases (%) (n = 2 874)	Controls (%) (n = 17 244)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Metformin				
No prior use	2 762 (96.1)	16 442 (95.4)	1.00 (referent)	1.00 (referent)
Any use	112 (3.9)	802 (4.7)	0.83 (0.67–1.01)	0.84 (0.61–1.15)
1–29	62 (2.2)	407 (2.4)	0.90 (0.69–1.18)	0.87 (0.61–1.24)
≥30	50 (1.7)	395 (2.3)	0.75 (0.55–1.01)	0.80 (0.53–1.22)
Sulphonylurea				
No prior use	2 778 (96.7)	16 573 (96.1)	1.00 (referent)	1.00 (referent)
Any use	96 (3.3)	671 (3.9)	0.85 (0.68–1.06)	0.92 (0.67–1.26)
1–29	49 (1.7)	314 (1.8)	0.93 (0.68–1.26)	0.98 (0.67–1.42)
≥30	47 (1.6)	357 (2.1)	0.78 (0.58–1.07)	0.87 (0.59–1.30)
Insulin				
No prior use	2 836 (98.7)	16 983 (98.5)	1.00 (referent)	1.00 (referent)
Any use	38 (1.3)	261 (1.5)	0.87 (0.62–1.23)	0.92 (0.63–1.35)
TZD				
No prior use	2 856 (99.4)	17 068 (99.0)	1.00 (referent)	1.00 (referent)
Any use	18 (0.6)	176 (1.0)	0.61 (0.37–0.99)	0.65 (0.38–1.11)

BMI, body mass index; CI, confidence interval; OR, odds ratio; TZD, thiazolidinediones.

*Adjusted for all other medications in this table, BMI, smoking and a diagnosis of diabetes mellitus.

Table 3. Odds ratios for head and neck cancer in relation to number of prescriptions for antidiabetic drug in the subgroup of cases and controls with a recorded diagnosis of diabetes mellitus.

Drugs and no. prescriptions	Cases (%) (n = 214)	Controls (%) (n = 1 273)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Metformin				
No prior use	103 (48.1)	560 (44.0)	1.00 (referent)	1.00 (referent)
Any use	111 (51.9)	713 (56.0)	0.84 (0.61–1.15)	0.91 (0.64–1.29)
1–29	61 (28.5)	392 (30.8)	0.84 (0.59–1.21)	0.90 (0.61–1.32)
≥30	50 (23.4)	321 (25.2)	0.83 (0.56–1.24)	0.92 (0.58–1.45)
Sulphonylurea				
No prior use	119 (55.6)	697 (54.8)	1.00 (referent)	1.00 (referent)
Any use	95 (44.4)	576 (45.3)	0.98 (0.72–1.33)	1.06 (0.75–1.50)
1–29	48 (22.4)	286 (22.5)	1.00 (0.69–1.44)	1.07 (0.72–1.57)
≥30	47 (22.0)	290 (22.8)	0.96 (0.65–1.41)	1.06 (0.68–1.65)
Insulin				
No prior use	176 (82.2)	1 053 (82.7)	1.00 (referent)	1.00 (referent)
Any use	38 (17.8)	220 (17.3)	0.99 (0.65–1.51)	0.97 (0.62–1.51)
TZD				
No prior use	196 (91.6)	1 134 (89.1)	1.00 (referent)	1.00 (referent)
Any use	18 (8.4)	139 (10.9)	0.74 (0.43–1.26)	0.74 (0.42–1.30)

OR, odds ratio; CI, confidence interval; TZD, thiazolidinediones.

*Adjusted for each other, BMI, smoking and diabetes duration.

than 8 years. Similarly, 96% of controls had more than a 4-year history of diabetes, and 65% had more than 8 years.

Stratification into different cancer entities revealed a decreased risk of laryngeal cancer associated with long-term metformin use (adjusted OR 0.41, 95% CI 0.17–1.03, based on 9 cases and 123 controls), while long-term use of metformin was not associated with the risk of cancer of the oral cavity or of pharyngeal cancer (Table 4).

The use of sulphonylureas or insulin or thiazolidinediones was not associated with a statistically significant altered risk of HNC in the main analysis or in the various sensitivity analyses.

Discussion

In this large population-based analysis, diabetes mellitus was not associated with an altered risk of HNC regardless of diabetes duration. Use of metformin and other antidiabetic drugs was not associated with a meaningfully decreased risk of overall HNC. Although we observed a marginally, however not statistically significant, decreased risk of HNC in long-term users in the main analysis, no such decreased risk was observed in the sensitivity analysis restricted to cases and controls with diabetes mellitus. There was, however, a suggestion of a decreased risk of laryngeal cancer in the long-term metformin users although this result was not statistically significant.

Table 4. Odds ratios for head and neck cancer subgroups in relation to number of prescriptions for metformin.

No. metformin prescriptions	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Oral cavity	(n = 1 206)	(n = 7 236)		
No prior use	1 157 (95.9)	6 923 (95.7)	1.00 (referent)	1.00 (referent)
Any use	49 (4.1)	313 (4.3)	0.83 (0.67–1.01)	0.78 (0.48–1.27)
1–29	21 (1.7)	159 (2.2)	0.79 (0.50–1.25)	0.65 (0.36–1.16)
≥30	28 (2.8)	154 (2.1)	1.09 (0.72–1.65)	1.02 (0.57–1.85)
Pharynx	(n = 570)	(n = 3 420)		
No prior use	552 (96.8)	3 269 (95.6)	1.00 (referent)	1.00 (referent)
Any use	18 (3.2)	151 (4.4)	0.83 (0.67–1.01)	0.93 (0.42–2.04)
1–29	7 (1.2)	90 (2.6)	0.46 (0.21–1.00)	0.61 (0.23–1.62)
≥30	11 (1.9)	61 (1.8)	1.04 (0.54–2.01)	1.49 (0.58–3.86)
Larynx	(n = 680)	(n = 4 080)		
No prior use	647 (95.2)	3 870 (94.9)	1.00 (referent)	1.00 (referent)
Any use	33 (4.9)	210 (5.2)	0.83 (0.67–1.01)	0.94 (0.51–1.75)
1–29	24 (3.5)	87 (2.1)	1.53 (1.03–2.60)	1.37 (0.71–2.62)
≥30	9 (1.3)	123 (3.0)	0.44 (0.22–0.87)	0.41 (0.17–1.03)

OR, odds ratio; CI, confidence interval.

*Adjusted for use of sulphonylurea, insulin and thiazolidinediones, BMI, smoking and a diagnosis of diabetes mellitus; results for cancer of the nasal cavity and unspecified HNC not shown.

Our observations regarding no association of diabetes and HNC are consistent with previously reported findings [15,16]. However, both decreased and increased risks have been reported for HNC overall and for some cancer subcategories in association with diabetes mellitus [13,14,17]. Only one study analysed the influence of diabetes duration on the risk of HNC, and also reported no effect of diabetes duration on HNC risk [15]. To the best of our knowledge, no other observational study has yet been published, exploring the risk of HNC related to antidiabetic drug treatment. However, data from *in vitro* and *in vivo* studies reported an association between HNC risk and deregulated mTOR pathway as well as beneficial effects of metformin on HNC cancer development [22–24]. Compared to cancers of the oral cavity and of the pharynx, the observed decreased RR estimate for laryngeal cancer in association with the long-term use of metformin is notable. However, these results must be interpreted with caution as they are based on a limited number of cases and controls. Furthermore, neither there have been any mechanistic studies of antiproliferative effects of metformin exclusively in laryngeal cancer cell lines nor have there been results reported specifically for laryngeal cancer in animal models.

This study has several limitations: malignant neoplasms develop gradually over a period of time and it is impossible to establish a precise date of onset. However, by shifting the index date 2 years backwards in time we increased the likelihood that exposure to antidiabetic drugs preceded the development of HNC. We thereby reduced the risk of protopathic bias, that is that we observed the effect of a drug being prescribed for an early manifestation of a disease that has not yet been diagnosed. Shifting the index date also accounted for a certain latency period of clinically detectable HNC, and we minimized the risk of a change of antidiabetic drug treatment due to evolving cancer in cases but not in controls. We may have included some misclassified HNC cases in this study. In an attempt to validate

the reported cancer diagnoses, we searched for documented cancer therapies or oncologic interventions and found 84% of the cancer cases to have such a recording after their cancer diagnosis. In the CPRD, cancer diagnoses are generally of a high validity [35]. The findings of the analysis restricted to cases with a high likelihood of a valid HNC diagnosis were closely similar to the overall results.

We were able to evaluate the role of many potential confounders in this study including BMI and smoking, as well as of a range of comorbid conditions and prescriptions for other drugs. However, we cannot exclude the possibility of residual confounding by, for example, discrepancies in nutrition, ethnicity or by differences in socioeconomic status (SES) between cases and controls. By matching cases and controls on general practice, we controlled at least partially for confounding by SES, as patients from the same neighbourhood are probable to attend the same general practice. Another limitation of our analysis is the high number of unknown values for BMI. However, the percentage of missing values was substantially lower in the sensitivity analysis restricted to diabetic patients, and in a sensitivity analysis restricted to patients with recorded BMI we observed closely similar findings.

There are several strengths of this study: we were able to use a well-established primary care database of high quality and completeness for this study. All information on drug use and disease diagnoses was recorded prospectively and independent of a study hypothesis, thus eliminating the possibility of recall bias. Furthermore, by excluding all patients with <3 years of recorded history in the database prior to the index date, we reduced the risk of including prevalent rather than incident cancer cases. As cases and controls had a comparable duration of diabetes history in each metformin exposure category, time window bias did not distort our findings. Finally, in addition to the main analysis, we ran sensitivity analyses restricted to cases and controls with diagnosed diabetes or restricted to cases

with additional recorded information regarding their cancer diagnosis, all of which yielded similar results.

Before inferring definite clinical implications from the results of this study, additional data from large studies are desirable. It would be premature to recommend clinical studies on prophylactic use of metformin in individuals with an increased risk of HNC or laryngeal cancer in particular. However, it is reassuring that none of the antidiabetic drugs analysed were associated with a suggestion of an increased HNC risk.

In conclusion, in this population-based study we did not find evidence for a materially altered risk of HNC overall in association with antidiabetic drug use. However, based on a limited number of cases and controls, we observed a decreased risk of laryngeal cancer in long-term users of metformin.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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