15th August 2023

To examine the impact of additional confounder adjustment for the potential association between second line T2DM therapy and thyroid cancer

Administrative details of the data analysis	
Substance(s)	GLP-1 RA
Condition/ADR(s)	T2DM
Short title of topic	T2DM therapy and thyroid cancer association
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1. Rationale and background

2. Thyroid cancer was thought to have an average estimated age standardized incidence in Europe of 12.7 per 100 000 person years in 2020.[1] The US Food and Drug Administration has contraindicated Glucagon-like peptide-1 agonists (GLP-1 RA) in patients with a personal or family history of medullary thyroid cancer based on preclinical and clinical findings.[2,3] GLP-1 receptor are expressed in thyroid tissues, and carcinogenicity studies in rodents have demonstrated a dose- and duration-dependent risk of medullary thyroid cancer with GLP-1 RA exposure.[4,5] However the association is not clearly established in humans given the long latency period for cancer induction and relatively low incidence of thyroid cancer.

3. GLP-1 RAs, including exenatide, liraglutide, dulaglutide, and semaglutide, are second-line drugs commonly used in the management of type 2 diabetes mellitus (T2DM). They induce direct activation of the GLP-1 receptor, which stimulates pancreatic insulin secretion in a glucose-dependent manner, while also inhibiting glucagon secretion.[6] A recent nested case-control analysis performed in the French national health care insurance system (SNDS) database (Bezin et al, 2023) showed an association with an increased risk of all thyroid cancer and medullary thyroid cancer with use of Glucagon-like peptide-1 agonists (GLP-1 RA) in people with T2DM, in particular after 1–3 years of cumulative treatment.[7] However, it was not possible to adjust for certain potential confounders in the association with thyroid cancer that were not captured in that database, such as smoking status or body mass index. Such risk factors generally have well known associations with cancer incidence.[8] In a UK study, nearly four in ten cancer cases have been attributed to known risk factors and understanding modifiable risk factors is therefore a key driver of changing cancer incidence.[9] Other known risk factors for thyroid cancer include exposure to radiation, family history, and other thyroid related conditions.

4. Our study aims to examine the potential impact of adjusting for missing confounders on the association with thyroid cancer in people with T2DM by attempting to reproduce the design of the French NCCS study.

5. Research question and objectives

To examine the impact of additional confounder adjustment for the association between T2DM therapy and thyroid cancer.

1. To calculate crude and adjusted effect estimates for GLP1-agonists (+/- other second-line T2DM therapy) and the association with thyroid cancer based upon the design for confounding adjustment in the study by Bezin et al. study.

2. To determine the impact of additional adjustment for smoking status, BMI, history of alcohol use/abuse on the effect estimates for GLP1-agonists (+/- other second-line T2DM therapy) and the association with thyroid cancer thyroid cancer.

6. Research methods

6.1. Study design

This primary analysis will be a case control study, nested in a cohort of patients diagnosed with T2DM treated with second-line antidiabetic therapy.

Cases will be the first thyroid cancer diagnosis after cohort entry.

Up to 50 **controls** per case will be then selected through incidence density sampling method.

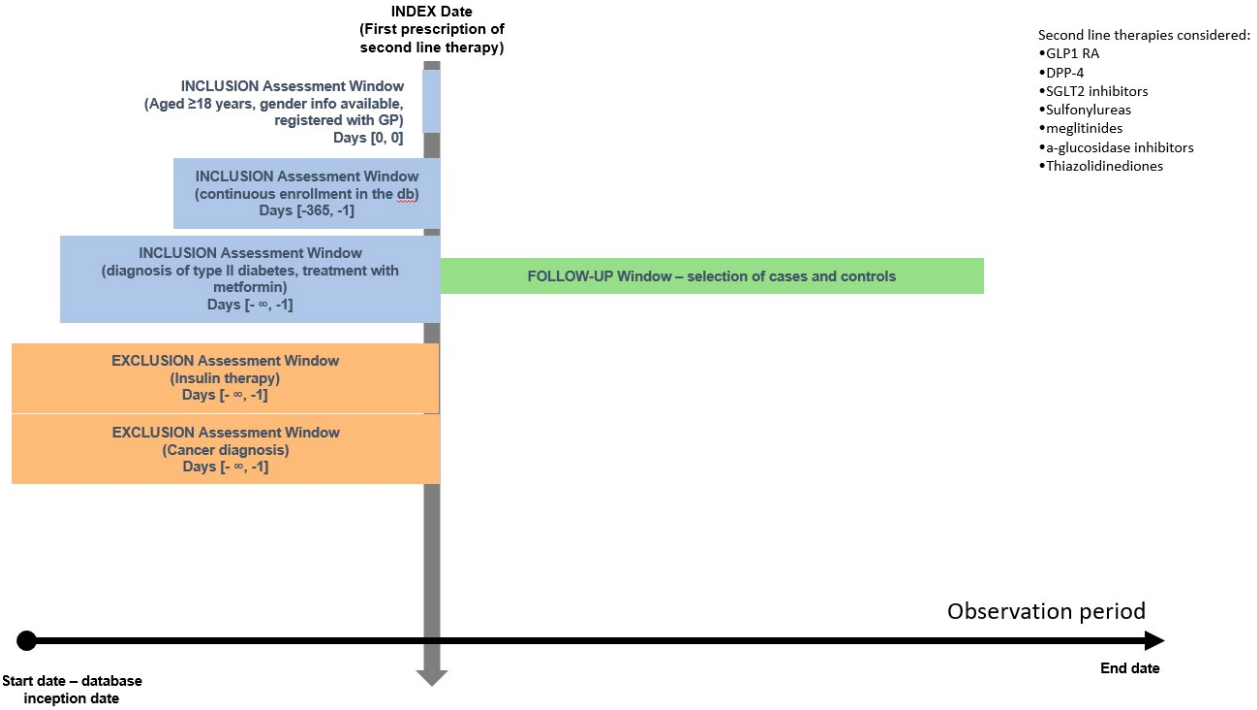

Figure 1 The design of the T2DM parent cohort

6.2. Data sources

The following databases will be used: IQVIA™ Medical Research Data (IMRD) UK. A brief description of this database is provided in Annex 1.

6.3. Setting and study population

For the primary analysis, the study population will be identified from the general population (UK) applying the following inclusion criteria for the creation of underlying cohort (T2DM 2nd line+ cohort):

Inclusion criteria:

- type II diabetes mellitus diagnosis
- previously treated with metformin
- currently treated with second line therapy such as: GLP1 RA, DPP-4, SGLT2 inhibitors, sulfonylureas, meglitinides, a-glucosidase inhibitors, thiazolidinediones

Exclusion criteria:
- Any use of insulin therapy prior to cohort entry
- Patients with any cancer diagnosis prior to cohort entry

Protocol amendment – The analysis excluded patients with a prior history of thyroid malignancy. However, given the limited number of cases patients we did not exclude patients with prior history of any other type of cancer.

6.4. Study period

Study period will be 1st January 2007 until 31st December 2022.

6.5. Variables

Outcome:

Any thyroid cancer diagnosis

Second-line therapy exposure:

Exposure for the following classes will be considered as second-line T2DM therapy: GLP1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors, Thiazolidinediones and sulfonylureas, meglitinides, or a-glucosidase inhibitors.

For each exposure class type

Definition 1

- Nonuser = no prior exposure record
- Current user = prescription within 90 days prior to the lag time period
- Past user = exposure >90 days before the lag time period
- Any history of use

Definition 2

- Nonuser = no prior exposure record
- Cumulative duration of use
    - o <1 year of use
    - o 1-3 years of use
    - o >3 years of use

Confounders:

Adjustment based upon the design by Bezin et al.:

- indices of multiple deprivation (IMD)
- goiter, hypo- and hyperthyroidism in the last year

- use of other antidiabetes drugs by therapeutic class

The primary **additional** confounders to be adjusted for will include:

- smoking status
- BMI
- history of alcohol abuse/misuse

Furthermore, the following confounders will also be considered depending on the impact of the primary additional confounders on the effect estimates and available time to conduct the analysis: Exposure to ciclosporin/tacrolimus, and history of HIV/AIDs, chronic kidney disease, rheumatoid arthritis and inflammatory bowel disease.

Lag time - A six-month lag time period prior to index date will be implemented whereby exposure recorded during this lag period will not be counted in the analysis.

6.6. Statistical analysis

6.6.1. Main statistical methods

Controls will be sampled through risk set sampling, matched for age, gender, cohort follow-up, and diabetes duration. The matching approach may be refined depending on the feasibility to identify controls. Conditional logistic regression will be used to examine the association between each exposure and outcome. Odds ratios in this context can be considered akin to rate ratios.

6.6.2. Sensitivity analysis

1. Varying the definition of the T2DM cohort:

As the number of thyroid cancer cases will be low, we may undertake the analysis by broadening the definition of the T2DM population to include:

- T2DM 1st line+ cohort - first-line treated T2DM or second-line treated T2DM patients
- T2DM Broad cohort - diet controlled T2DM or first-line treated T2DM or second-line treated T2DM

2. Varying the lag period: 3 months, 12 months, 24 months (depending upon the impact of confounder adjustment on the primary analysis).

Protocol amendment – the varying of lag period analysis was not performed, since the number of cases was low, it was considered of no additional value.

6.7. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

7. Results

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database) were removed prior to publication of this report. Additional cells have been redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

7.1. Descriptive data

Of 64,101 patients eligible for the T2DM 2nd line+ cohort, 23 incident thyroid cancer cases were matched to 1083 controls with an incidence of thyroid cancer of 5.6 per 100,000 person years (pys). Characteristics of the cases and matched controls for each cohort are shown in Table 1. GLP1RA exposure among thyroid cancer cases was low and occurred in fewer than five patients. Among controls, any prior GLP1RA exposure occurred in 13.0% of patients from the control group. Prior history of thyroid disorder (hyperthyroidism, hypothyroidism, or goitre) was more prevalent among thyroid cancer cases than controls. Distribution of smoking status, history of alcohol misuse disorder and BMI were generally similar between cases and controls. Missing data on smoking status and BMI was very low.

Table 1 Characteristics of cases and controls from the T2DM second-line cohort

Characteristic	Cases	Controls
Number	23	1083
Female (%)	15 (65.2)	722 (66.7)
Age* (%)	67.7 (8.1)	67.2 (7.5)
IMD (%)		
• 1	<6	126 (11.6)
• 2	<6	160 (14.8)
• 3	<6	163 (15.1)
• 4	<6	143 (13.2)
• 5	<6	111 (10.3)
• 6	<6	77 (7.1)
• 7	<6	81 (7.5)
• 8	<6	82 (7.6)
• 9	<6	61 (5.6)
• 10	<6	78 (7.2)
• Missing	0	<6
GLP1RA (%)	<6	141 (13.0)
DPP4i (%)	12 (52.2)	553 (51.1)
SGLT2i (%)	<6	217 (20.0)
Sulfonylureas (%)	16 (69.6)	835 (77.1)
Metformin (%)	23 (100.0)	1072 (99.0)
Glitazone (%)	6 (26.1)	292 (27.0)
Glinide (%)	<6	22 (2.0)
Insulin (%)	<6	169 (15.6)
Alpha-glucosidase (%)	0	0

Characteristic	Cases	Controls
Thyroid disorder*	8 (34.8)	164 (15.1)
Smoking status (%)		
• Current	<6	132 (12.2)
• Ex-smoker	7 (30.4)	360 (33.3)
• Non-smoker	13 (56.6)	590 (54.5)
• Missing smoking status	<6	<6
Alcohol misuse disorder (%)	<6	35 (3.2)
BMI (mean (SD))	31.4 (5.8)	32.1 (8.4)
• Missing BMI value	<6	6 (0.6)

* - hyperthyroidism, hypothyroidism, or goitre, mean. SD=standard deviation. BMI=body mass index. IMD=index of multiple deprivation. IMD1=most affluent. IMD10=least affluent. Cell counts <6 unable to disclose for governance reasons.

Secondary analysis was performed in cases and controls nested within two other cohorts specified in the sensitivity analysis namely the T2DM 1st line cohort and T2DM Broad cohort. Of 97,613 patients in the T2DM 1st line cohort, 38 incident thyroid cancer cases were matched to 1865 controls with the same incidence of thyroid cancer of 5.9 per 100,000 pys. Of 125,486 patients in the T2DM Broad cohort, 43 incident thyroid cases were matched to 2,095 controls with a similar incidence of thyroid cancer of 6.2 per 100,000 pys. GLP1RA exposure among cases was similar to cases in the T2DM second-line cohort (Supplementary tables 1 and 2), while in controls, GLP1RA exposure occurred in 9.3% and 6.9% of controls respectively. The occurrence of prior history of thyroid disorder and missing data on smoking status and BMI were also similar.

7.2. Main results

Association between thyroid cancer and smoking status, BMI and alcohol misuse disorder

The crude association between thyroid cancer and smoking status, BMI and alcohol misuse disorder is shown in Table 2. There was no strong evidence of an association between smoking status, BMI or alcohol misuse disorder and incident thyroid cancer in cases and controls sampled from the T2DM 2nd line cohort, T2DM 1st line or T2DM Broad cohort, although 95% confidence intervals of the effect estimates were wide.

Table 2 Crude association between smoking status, BMI and history of alcohol misuse disorder and incident thyroid cancer in each cohort

Characteristics	Crude IRR (95%CI)		
	T2DM 2nd line	T2DM 1st line	T2DM Broad
Smoking status			
• Non-smoker	Reference	Reference	Reference
• Ex-smoker	0.86 (0.33 - 2.23)	0.86 (0.42 - 1.76)	1.06 (0.55 - 2.07)
• Current	1.04 (0.29 - 3.71)	0.50 (0.15 - 1.68)	0.73 (0.25 - 2.13)
BMI	0.99 (0.94 - 1.05)	1.00 (0.95 - 1.05)	0.99 (0.95 - 1.04)
Alcohol misuse disorder	2.97 (0.66 - 13.32)	1.05 (0.25 - 4.47)	1.04 (0.24 - 4.41)

BMI=Body mass index modelled as a continuous variable. T2DM=type 2 diabetes mellitus. IRR=incidence rate ratio. CI=confidence interval.

Impact adjusting for smoking status, BMI and alcohol misuse disorder on the association between incident thyroid cancer and different classes of T2DM treatments

Effect estimates for the association between different classes of T2DM treatments and incident thyroid cancer from the T2DM 2nd line+ cohort are shown in Table 3. Adjustment was first performed by

including different classes of T2DM treatments among cases and controls that had been matched on age, gender and duration of diabetes (Model 1). The effect estimate for any prior GLP1RA exposure and incident thyroid cancer using Model 1 was IRR 0.26 (0.03 - 2.06) for patients from the T2DM 2nd line+ cohort. The effect estimates for any prior DPP4i exposure and any prior SGLT2i exposure using Model 1 were IRR 0.89 (0.37 - 2.17) and IRR 0.84 (0.25 - 2.86) respectively.

Table 3. Adjusted incidence rate ratios of thyroid cancer by prescription of antidiabetic drugs, by drug class

	IRR (95%CI)		
Exposure	Model 1	Model 2	Model 3
GLP1RA	0.26 (0.03 - 2.06)	0.27 (0.04 - 2.15)	0.24 (0.03 - 2.04)
DPP4i	0.89 (0.37 - 2.17)	0.84 (0.34 - 2.07)	0.83 (0.34 - 2.07)
SGLT2i	0.84 (0.25 - 2.86)	0.82 (0.24 - 2.85)	0.88 (0.25 - 3.04)
Sulfonylureas	0.61 (0.21 - 1.75)	0.60 (0.20 - 1.78)	0.54 (0.18 - 1.62)
Metformin	-		
Glitazone	0.92 (0.31 - 2.75)	1.02 (0.33 - 3.14)	1.24 (0.39 - 3.92)
Glinide	1.92 (0.22 - 17.00)	2.11 (0.24 - 18.37)	2.79 (0.30 - 25.81)
Insulin	2.07 (0.67 - 6.39)	1.98 (0.63 - 6.24)	2.21 (0.68 - 7.18)

Model 1 - adjusted for age, sex, duration of diabetes. Model 2 – as model 1 plus adjustment for prior history of thyroid disorder and index of multiple deprivation score, Model 3 – as model 2 plus adjustment for smoking status, BMI and prior history of alcohol use disorder; BMI - Body mass index. T2DM -type 2 diabetes mellitus. IRR=incidence rate ratio. CI=confidence interval., GLP1RA - Glucagon-like peptide-1 agonists, DPP4I – dipeptidylpeptidase-4 inhibitors, SGLT2i - Sodium/glucose cotransporter 1 inhibitors,

The effect estimates for any prior exposure to different classes of T2DM treatments adjusting for deprivation and history of thyroid disorder (Model 2) and deprivation, history of thyroid disorder, smoking status, BMI and history of alcohol misuse disorder (Model 3) demonstrated small changes in effect estimates compared to Model 1. Effect estimates from Model 3 were IRR 0.24 (0.03 - 2.04) for any prior GLP1RA exposure, IRR 0.83 (0.34 - 2.07) for any prior DDP4I exposure and IRR 0.88 (0.25 - 3.04) for any prior SGLT2i exposure.

For patients from the T2DM 1st line+ cohort, effect estimates for Model 1 were IRR 0.18 (0.02 - 1.49) for patients with any GLP1RA exposure, IRR 0.96 (0.43 - 2.15) for patients with any DPP4i exposure and IRR 1.20 (0.38 - 3.78) for patients with SGLT2i exposure (Supplementary Table 3). Effect estimates from Model 3 for patients from the 1st line cohort were IRR 0.20 (0.02 - 1.62) for any prior GLP1RA exposure, IRR 1.00 (0.44 - 2.30) for any prior DPP4I exposure and IRR 1.33 (0.42 - 4.23) for any prior SGLT2I exposure.

For patients from the T2DM Broad cohort, effect estimates for Model 1 were 0.23 (0.03 - 1.78) for patients with any prior GLP1RA exposure, IRR 1.25 (0.57 - 2.76) for patients with any prior DPP4i exposure and IRR 1.02 (0.32 - 3.23) for patients with any prior SGLT2i exposure (Supplementary Table 4). Effect estimates from Model 3 for patients from the any T2DM cohort were 0.20 (0.02 - 1.62) for patients with any prior GLP1RA exposure, IRR 1.00 (0.44 - 2.30) for patients with any prior DPP4I exposure and IRR 1.33 (0.42 - 4.23) for patients with any prior SGLT2i exposure.

The impact of additional confounder adjustment on the effect estimates for other classes of T2DM treatments followed a similar pattern (Table 3 and Supplementary Tables 3 and 4).

7.3. Other analyses, including sensitivity analyses

The results for alternative cohorts, T2DM 1st line cohort and T2DM Broad cohort are presented in the main results to facilitate comparison, while the description thereof are in Supplementary tables 1 and 2. Varying the lag period was not performed as a sensitivity analysis, since very few cases were retrieved in the main analysis and therefore the additional value of this sensitivity analysis was considered limited.

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8. Discussion

8.1. Key results and interpretation

This study did not find an association between GLP1RA and thyroid cancer, however a significant association between any class of T2DM treatments and incident thyroid cancer cannot be excluded from this analysis considering the lack of power.

However, the objective of the study was not to quantify the association between GLP1RA treatment and incident thyroid cancer, but rather to examine whether additional confounder adjustment potentially has a strong impact on the size and direction of any association to inform whether observed associations among existing studies failing to adjust for these variables would explain the results. The risk factors for thyroid cancer are not well established, except for exposure to radiation, family history, thyroid condition diagnosed previously and BMI.[2]

Despite the imprecise nature of the effect estimates, we observed limited evidence to suggest that additional adjustment for smoking status, BMI and history of alcohol misuse disorder has a strong impact on the size and direction of an association between any prior exposure to different classes of T2DM treatments and incident thyroid cancer.

8.2. Limitations

The main limitation is that number of incident thyroid cancer cases was extremely limited and the study was underpowered.

Exposure to T2DM treatments was based on prescriptions issued by general practices in the UK and treatments issued by hospital pharmacies are not captured.

The analysis excluded patients with a prior history of thyroid malignancy. However, given the limited number of cases patients we did not exclude patients with prior history of any other type of cancer.

No validation of incident thyroid cancer diagnosis has been performed and the recording of thyroid cancer is assumed to be accurate. This similarly applies to other patient conditions and exposures.

9. Conclusion

Additional adjustment for smoking status, BMI and history of alcohol misuse disorder did not have a strong impact on the size and direction of an association between any prior exposure to different classes of T2DM treatments and incident thyroid cancer.

10. References

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Annex 1 -Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

Annex 2 - Supplementary tables

Supplementary table 1. Characteristics of cases and controls from the T2DM 1st line+ cohort

Characteristic	Cases	Controls
Number	38	1865
Female (%)	26 (68.4)	1300 (69.7)
Age* (%)	66.76 (9.5)	67.3 (9.6)
IMD (%)		
• 1	<6	232 (12.4)
• 2	6 (15.8)	268 (14.4)
• 3	<6	260 (13.9)
• 4	7 (18.4)	220 (11.8)
• 5	<6	160 (8.6)
• 6	<6	147 (7.9)
• 7	<6	149 (8.0)
• 8	<6	181 (9.7)
• 9	<6	104 (5.6)
• 10	6 (15.8)	142 (7.6)
• Missing	0	<6
GLP1 (%)	<6	173 (9.3)
DPP4 (%)	12 (31.6)	604 (32.4)
SGLT2 (%)	<6	206 (11.1)
SU (%)	16 (42.1)	870 (46.7)
Biguanide (%)	37 (97.4)	1798 (96.4)
Glitazone (%)	6 (15.8)	244 (13.1)
Glinide (%)	<6	21 (1.1)
Insulin (%)	5 (13.2)	164 (8.8)
Alpha-glucosidase (%)	0	0
Thyroid disorder*	12 (31.6)	287 (15.4)
Smoking status (%)		
• Current	<6	258 (13.8)
• Ex-smoker	12 (31.6)	605 (32.5)
• Non-smoker	23 (60.5)	1001 (53.7)
• Missing smoking status	0	
Alcohol misuse disorder (%)	<6	90 (4.8)
BMI (mean (SD))	31.5 (5.05)	31.8 (7.1)
• Missing BMI value	<6	11 (0.6)

SD=standard deviation. BMI=body mass index.
IMD=index of multiple deprivation. IMD1=most affluent. IMD10=least affluent.
Cell counts <6 unable to disclose for governance reasons.

Supplementary table 2. Characteristics of cases and controls from the T2DM broad cohort

Characteristic	Cases	Controls
Number	43	2095
Female (%)	28 (65.1)	1400 (66.8)
Age* (%)	68.5 (10.6)	68.1 (10.7)
IMD (%)		
• 1	<6	236 (11.3)
• 2	7 (16.3)	327 (15.6)
• 3	<6	294 (14.)
• 4	8 (18.6)	241 (11.5)
• 5	<6	185 (8.8)
• 6	<6	171 (8.2)
• 7	<6	184 (8.8)
• 8	5 (11.6)	161 (7.7)
• 9	<6	133 (6.4)
• 10	7 (16.3)	160 (7.6)
• Missing	0	<6
GLP1 (%)	<6	145 (6.9)
DPP4 (%)	12 (27.9)	524 (25.0)
SGLT2 (%)	<6	208 (9.9)
SU (%)	16 (37.2)	842 (40.2)
Biguanide (%)	38 (88.4)	1658 (79.1)
Glitazone (%)	6 (14.0)	234 (11.2)
Glinide (%)	<6	18 (0.9)
Insulin (%)	5 (11.6)	183 (8.7)
Alpha-glucosidase (%)	0	0
Thyroid disorder*	13 (30.2)	284 (13.6)
Smoking status (%)		
• Current	<6	266 (12.7)
• Ex-smoker	15 (34.9)	672 (32.1)
• Non-smoker	24 (55.8)	1156 (55.2)
• Missing smoking status	0	<6
Alcohol misuse disorder (%)	<6	90 (4.3)
BMI* (SD)	30.3 (5.2)	31.9 (7.1)
• Missing BMI value	<6	14 (0.7)

Supplementary table 3. Association between different classes of T2DM treatments and incident thyroid cancer inT2DM patients from the T2DM 1st line cohort

	IRR (95%CI)		
Exposure	Model 1	Model 2	Model 3
GLP1	0.18 (0.02 - 1.49)	0.19 (0.02 - 1.8)	0.20 (0.02 - 1.62)
DPP4i	0.96 (0.43 - 2.15)	0.97 (0.43 - 2.18)	1.00 (0.44 - 2.30)
SGLT2i	1.20 (0.38 - 3.78)	1.32 (0.41 - 4.20)	1.33 (0.42 - 4.23)
Sulfonylureas	0.77 (0.35 - 1.67)	0.79 (0.36 - 1.74)	0.71 (0.31 - 1.60)
Metformin	1.56 (0.18 - 13.28)	1.51 (0.17 - 13.38)	1.51 (0.17 - 13.38)
Glitazone	1.24 (0.43 - 3.58)	1.35 (0.45 - 4.04)	1.62 (0.54 - 4.91)
Glinide	2.06 (0.24 - 17.58)	2.39 (0.28 - 20.77)	2.76 (0.30 - 25.06)

Model 1 - Model adjusted for age, sex, duration of diabetes.
Model 2 - Model 1 plus adjustment for prior history of thyroid disorder and index of multiple deprivation score,
Model 3 - Model 2 plus adjustment for smoking status, BMI and prior history of alcohol use disorder
BMI - Body mass index. T2DM - type 2 diabetes mellitus. IRR=incidence rate ratio. CI=confidence interval.

Supplementary table 4. Association between different classes of T2DM treatments and incident thyroid cancer in patients from the T2DM Broad cohort

	IRR (95%CI)		
Exposure	Model 1	Model 2	Model 3
GLP1	0.23 (0.03 - 1.78)	0.24 (0.03 - 1.91)	0.24 (0.03 - 1.92)
DPP4	1.25 (0.57 - 2.76)	1.28 (0.57 - 2.86)	1.25 (0.55 - 2.82)
SGLT2	1.02 (0.32 - 3.23)	0.97 (0.30 - 3.15)	0.96 (0.29 - 3.12)
Sulfonylureas	0.65(0.31 - 1.38)	0.64 (0.30 - 1.36)	0.61 (0.28 - 1.34)
Metformin	2.16 (0.81 - 5.78)	2.25 (0.84 - 6.05)	2.82 (0.95 - 8.38)
Glitazone	1.35 (0.50 - 3.69)	1.50 (0.54 - 4.19)	1.80 (0.62 - 5.21)
Glinide	2.97 (0.35 - 25.18)	2.37 (0.28 - 19.82)	3.57 (0.40 - 32.21)
Insulin	1.60 (0.55 - 4.69)	1.65 (0.55 - 4.92)	1.65 (0.55 - 4.96)

Model 1 Model adjusted for age, sex, duration of diabetes.
Model 2 –Model 1 plus adjustment for prior history of thyroid disorder and index of multiple deprivation score,
Model 3 - Model 2 plus adjustment for smoking status, BMI and prior history of alcohol use disorder
BMI=Body mass index. T2DM=type 2 diabetes mellitus. IRR=incidence rate ratio. CI=confidence interval.