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Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim: To conduct a meta-analysis of randomized clinical trials (RCTs) to investigate whether there is an association between glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment and thyroid cancer.

Materials and Methods: In this meta-analysis of RCTs, we included studies comparing a GLP-1RA with any comparator, lasting at least 52 weeks, and reporting the incidence of adverse events independently of the principal endpoint and population. All cases of thyroid cancer were collected.

Results: We retrieved 64 trials, 26 of which reported at least one incident case of thyroid cancer. GLP-1RA treatment was associated with a significant increase in the risk of overall thyroid cancer (Mantel-Haenzel odds ratio [MH-OR] 1.52 [95% confidence interval {CI} 1.01, 2.29]; $P = 0.04$, $I^2 = 0\%$), with a fragility index of 1, and a 5-year number needed to harm of 1349. The association remained significant when including only trials lasting at least 104 weeks (MH-OR 1.76 [95% CI 1.00, 3.12]; $P = 0.05$). No significant association was found for papillary thyroid cancer (MH-OR 1.54 [95% CI 0.77, 3.06]; $P = 0.22$) or medullary thyroid cancer (MH-OR 1.44 [95% CI 0.23, 9.16]; $P = 0.55$).

Conclusions: Our meta-analysis showed that GLP-1RA treatment could be associated with a moderate increase in relative risk for thyroid cancer in clinical trials, with a small increase in absolute risk. Studies of longer duration are required to assess the clinical implications of this finding.

KEYWORDS
glucagon-like peptide-1 receptor agonists, meta-analysis, obesity, thyroid cancer, type 2 diabetes mellitus

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used as a treatment for type 2 diabetes, due to their ability to improve glucose control without increasing hypoglycaemic risk. They have also been shown to reduce the incidence of cardiovascular events.[1,2] GLP-1RAs are increasingly prescribed for the treatment of overweight and obesity as they have been shown to reduce body weight to a greater extent than any other available non-surgical treatment.[3,4]

The safety of GLP-1RAs has been confirmed by large-scale randomized trials, usually with cardiovascular primary endpoints. In earlier phases of the development of GLP-1RAs, the main safety concerns were related to a possible increase in the risk of medullary thyroid carcinoma (MTC)[5] and pancreatitis.[6] Randomized trials failed to detect any increase in calcitonin levels[7,8] and did not confirm the risk of pancreatitis,[9] whereas a significant increase in cholelithiasis was highlighted.[10]

Some retrospective observational studies detected an increased risk of thyroid cancer in association with GLP-1RA treatment,[11,12] which was also confirmed by analyses of serious adverse events reported to the US Food and Drug Administration (FDA)[11,13] and the World Health Organization's pharmacovigilance database VigiBase.[12,14] Such an association is consistent with the results of some preclinical studies[15]: thyroid C cells express glucagon-like peptide-1 (GLP-1) receptors, and GLP-1 stimulates cell growth and calcitonin production in rodent models in vitro,[16] but these effects are smaller in humans.[5] In addition, GLP-1 receptors are expressed in human papillary thyroid carcinoma (PTC) cells[17] to a greater extent than in normal human thyroid cells.[18] Although GLP-1 receptor genetic polymorphism tissue expression has been linked to an increase in PTC incidence and invasiveness,[19] a significant effect of GLP-1RA agonists on the proliferation of PTC cells has not been demonstrated.[18] The pathophysiological rationale for a potential increase in the risk of thyroid cancer determined by GLP-1RA treatment cannot therefore be considered firmly established. In addition, epidemiological data suggesting such an association have methodological limitations, mostly related to the possibility of confounders unaccounted for in analysis[20–22]; furthermore, other observational studies did not confirm such association.[23] Evidence from randomized clinical trials (RCTs), which are not affected by the same limitations of observational studies, may be helpful in the assessment of this important safety issue. The aim of the present meta-analysis was to assess the possible association of GLP-1RA treatment with the risk of thyroid cancer in RCTs.

2 | MATERIALS AND METHODS

2.1 | Data sources and search strategy

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines[24] and the protocol was registered on the PROSPERO[25] website (registration number CRD42023456382).

We performed a Medline, Embase, Clinicaltrials.gov and Cochrane CENTRAL Database search up to 20 August 2023. Keywords included all the GLP-1RA drug names. Animal studies were excluded. No language or date restriction was imposed. Detailed information on the search strategy is reported in Table S1.

2.2 | Endpoints

The principal endpoint was the incidence of any thyroid cancer during the study; secondary endpoints were the incidence of PTC, the incidence of MTC, the incidence of follicular thyroid cancer, and the incidence of overall differentiated thyroid cancer.

2.3 | Study selection

We included all RCTs with a duration of follow-up of at least 52 weeks, in which any GLP-1RA approved by European Medical Agency for any indication (ie, type 2 diabetes or obesity) was compared with either placebo or active comparators in adults (older than 18 years). Trials were included if they reported data on the incidence of thyroid cancer or any other adverse event independently of the primary endpoint assessed in the study.

2.4 | Data extraction

A predetermined sheet was used to extract the variables of interest: the incidence of thyroid cancer (reported as 'thyroid cancer', 'papillary thyroid cancer', 'PTC', 'follicular thyroid cancer', 'medullary thyroid cancer', 'MTC', 'thyroid malignant tumour', 'thyroid tumour', 'thyroid neoplasm'); trial duration; mean age at baseline; body mass index (BMI) at baseline; and percentage of women enrolled. Estimates for the variables of interest at the end of follow-up were extracted from the principal publication, when available. When needed, secondary publications and the clinicaltrials.gov registry were used for retrieval of missing information, in the hierarchical order reported above. If any data on the endpoint were unavailable, an attempt was made to obtain this information by asking the corresponding author of the paper directly. Data extraction was performed independently by two of the authors (M.M., G.A.S), and conflicts were resolved by a third investigator (E.M.).

2.5 | Data analysis and quality assessment

The risk of bias in RCTs was assessed using the Cochrane recommended tool,[26] which includes seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Based on these results, the RCTs were graded as having 'low' risk of bias, 'high' risk of bias, or

'uncertain' risk of bias. Mantel-Haenzel odds ratios (MH-ORs) for categorial variables were calculated using random-effect models in case of significant heterogeneity and fixed- effect models if heterogeneity was not relevant; a sensitivity analysis was performed using a fixed-effect model in the case of significant heterogeneity, and a random-effect model if heterogeneity was not relevant. A further sensitivity analysis was performed with continuity correction, that is, adding one event for treatment arm in the trials with zero events. For the main analyses, a fragility index, that is, the minimum number of patients whose status would have to change from a non-event to an event required to turn a statistically significant result to a nonsignificant result,[27] was calculated through an iterative heuristic process. In each iteration, the status of one subject was changed from non-event to event in the control group in a study, and a new meta-analysis was performed; we chose the event status modification leading to the confidence interval (CI) closest to the null value. Based on this event status modification, we continued the iterative process until the CI based on a modified dataset covered the null. The fragility of this meta-analysis was derived as the total number of event status modifications in the foregoing iterative process; a smaller number indicates a more fragile result.[28] Statistical heterogeneity was assessed by the I^2 test, whereas Funnel plots were used to detect publication bias for principal endpoints with at least 10 trials. Separate analyses were performed for trials using different molecules, and for subgroups of studies based on trial duration (≤52 weeks, 53-103 weeks, and >103 weeks), BMI categories (mean BMI at baseline ≤32 kg/m^2 and >32 kg/m^2), patients' age (below or above the median age). The results of individual studies and the syntheses of meta-analyses are displayed as forest plots.

To estimate the 5-year number needed to harm (NNH), namely, the number of patients needed to be treated with a drug for 5 years to determine one additional case of thyroid neoplasm, was calculated, applying the effect of GLP-1RAs observed in clinical trials to the 5-year incidence of thyroid cancer, calculated according to the observed incidence of events in the control groups of the same trials. All analyses were performed using Review Manager (RevMan), version 5.4.1 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen) and SPSS 28.0.1.0 (IBM SPSS Statistics).

3 | RESULTS

3.1 | Characteristics of included trials

The complete trial research flow summary is reported in Figure S1 of the supplementary materials. Briefly, out of 815 items retrieved after removing duplicates, 94 were selected for retrieval of full text; of those, 30 records were excluded because the inclusion criteria were not satisfied, with one large trial,[29] in particular, not reporting data on the incidence of any cancer, and for which such information could not be retrieved. The number of studies fulfilling the inclusion criteria was 64, overall enrolling 46 228 patients on GLP-1RA treatment, and 38 399 subjects on placebo or a comparator. The trials were more often performed for the treatment of diabetes (48 trials), while 16 were performed for the treatment of obesity. Liraglutide was used in 26 trials, semaglutide in 17 trials, exenatide in 16 trials, dulaglutide in 9 trials; the comparators were placebo, insulin, dipeptidyl peptidase-4 inhibitors, sulphonylureas, and sodium-glucose cotransporter-2 inhibitors, no treatment or a treatment chosen by the investigators, for 36, 12, 6, 4, 3, 2 and 1 trial, respectively. The characteristics of the enrolled trials are reported in Table S2, and the list of excluded studies is reported in Table S3. The median and mean duration of the studies were 53 and 75 weeks, respectively. The median age was 56 years, the median BMI was 32 kg/m^2, and the median proportion of women enrolled was 50.3%. The risk of bias table and summary are reported in Figures S2 and S3, respectively. In brief, 27 trials were open-label, seven trials reported a possible attrition bias, and five trials showed possible issues related to the randomization process.

Twenty-six trials, enrolling 69 909 patients overall, reported at least one incident case of thyroid cancer (Table 1). Of the 86 cases of thyroid cancer retrieved (60 and 26 in the GLP-1RA and comparator arms, respectively), 25 (19 in the GLP-1RA arm vs. 6 in comparator arms) were reported as PTCs and three as MTCs (two with GLP-1RAs and one with comparators); the remainder of the thyroid cancer cases were reported as thyroid malignant neoplasms or cancer, without any further specifications. No cases of follicular or anaplastic neoplasms were specifically reported.

3.2 | Overall thyroid cancer

The visual analysis of funnel plots for overall thyroid cancer did not suggest any risk of publication bias (Figure S4). GLP-1RA treatment was associated with a significant increase in the risk of overall thyroid cancer in the fixed-effect analysis (MH-OR 1.52 [95% CI 1.01, 2.29]; $P = 0.04$ [Figure 1]), with no heterogeneity ($I^2 = 0\%$). The fragility index was 1, meaning that it would take only one additional case of thyroid cancer occurring in the comparator arm for the association to lose significance. In sensitivity analyses with a random-effect model (MH-OR 1.41 [95% CI 0.91, 2.17]; $P = 0.22$, $I^2 = 0\%$ [Figure S5]) and with continuity correction (MH-OR 1.15 [95% CI 0.86, 1.54]; $P = 0.36$ [Figure S6]), the association between GLP-1RA treatment and incident thyroid cancer was no longer significant. The leave-one-out analysis showed that the exclusion of none of the included studies modified the extent of the effect significantly, but five studies were identified[33,34,37,38,45] whose exclusion would lead to a nonsignificant result (Table S4). The incidence of thyroid cancer in the placebo group of the trials reporting patient-year observation time was 0.285/1.000 patient-years, which, applying the 52% increase observed in our meta-analysis, led to an estimated 0.148/1.000 patient-year absolute increase in risk for thyroid cancer in patients in GLP-1RA therapy; the corresponding 5-year NNH was 1349. If including all the trials, assuming patient-year as the product of the number of at-risk patients and the mean follow-up time, the incidence was 0.246/1.000 patient-years, leading to an estimated 5-year NNH of 1562.

TABLE 1 Characteristics of the included trials with at least one event of thyroid cancer.

Study name	Drug	Dose (mg)	Comparator	Ind	Dur	Age	F%	HbA1c	BMI	P-y drug	P-y control
Ahren 2017[30] (SUSTAIN-2)	Semaglutide	0.5–1 QWK	Sita	DM	56	55	49.4	8.1	32.5	*Nr*	*nr*
Buse 2020[31] (PIONEER-7	Semaglutide	7–14 QD	Sita	DM	52	57	43.5	7.9	31.0	*nr*	*nr*
Davies 2015[32] (SCALE D)	Liraglutide	1.8 QD	Placebo	DM	56	55	49.8	7.9	37.4	570	180
Garber 2011 (LEAD)[33]	Liraglutide	1.8 QD	Glimepiride	DM	104	53	50.3	8.3	33.0	1366	538
Gerstein 2019 (REWIND)[34]	Dulaglutide	1.5 QWK	Placebo	DM	281	66	46.3	7.3	32.3	25 277	24 925
Giorgino2015 (AWARD-2)[35]	Dulaglutide	1.5 QWK	Glarg	DM	78	57	48.7	8.1	31.3	*nr*	*nr*
Gough 2015 (DUAL-I)[36]	Liraglutide	1.8 QD	Degludec	DM	52	55	49.2	8.3	31.2	*nr*	*nr*
Holman 2017 (EXSCEL)[37]	Exenatide	2 QWK	Placebo	DM	166	62	38.0	8.0	31.7	22 676	22 625
Husain 2019 (PIONEER 6)[38]	Semaglutide	14 QD	Placebo	DM	68	66	31.6	8.2	32.0	2103	2055
Marso 2016 (SUSTAIN-6)[39]	Semaglutide	0.5–1 QWK	Placebo	DM	109	65	39.3	8.7	32.8	3333	3318
Marso 2016 (a) (LEADER)[40]	Liraglutide	1.8 QD	Placebo	DM	198	64	35.7	8.7	32.5	17 882	17 795
Nauck 2013 (LEAD-2)[41]	Liraglutide	1.8 QD	Glim/met	DM	104	57	41.3	8.6	31.2	*nr*	*nr*
O'Neill 2018 (NN9536)[42]	Liraglutide	3 QD	placebo	OB	52	47	64.1	5.5	39.3	*nr*	*nr*
Pfeffer 2015 (ELIXA)[43]	Lixisenatide	20 QD	Placebo	DM	107	60	30.7	7.6	30.1	6334	6444
Pratley 2019 (PIONEER-4)[44]	Liraglutide	1.8 QD	Placebo	DM	52	56	48.0	8.0	33.0	*nr*	*nr*
Pi-sunyer 2015 (SCALE OB)[45]	Liraglutide	3.0 QD	Placebo	OB	70	45	78.5	5.6	38.3	2237	1067
Rosenstock 2019 (PIONEER-3)[46]	Semaglutide	7–14 QD	Sita	DM	78	58	47.2	8.3	32.5	*nr*	*nr*
Ruff 2021 (FREEDOM)[47]	Exenatide	ITCA 0.06 QD	Placebo	DM	62	63	36.7	8.0	32.3	2879	2925
Unger 2022 (LIRA-PRIME)[48]	Liraglutide	1.8 QD	Any OAD	DM	104	57	47.6	8.2	33.5	1356	1258
Wadden 2013 (SCALE M)[49]	Liraglutide	3.0 QD	Placebo	OB	56	46	81.3	5.6	37.9	*nr*	*nr*
Wadden 2020 (SCALE IBT)[50]	Liraglutide	3.0 QD	Placebo	OB	56	47	82.9	5.5	39.0	*nr*	*nr*
Wadden 2021 (STEP-3)[51]	Semaglutide	2.4 QD	Placebo	OB	68	46	81.0	5.7	38.0	*nr*	*nr*
Wang 2019 (AWARD-C)[52]	Dulaglutide	0.75/1.5 QWK	Glargine	DM	52	55	64.1	8.4	26.0	*nr*	*nr*
Weinstock 2015 (AWARD-5)[53]	Dulaglutide	1.5 QWK	Sita	DM	104	54	53.5	8.1	31.0	*nr*	*nr*
Wilding 2021 (STEP-1)[54]	Semaglutide	2.4 QWK	Placebo	OB	68	46	74.0	5.6	37.9	1708	829
Yamada 2020 (PIONEER-9)[55]	Semaglutide	7–14 QD	Placebo	DM	52	61	22.3	8.2	26.0	192	49

Abbreviations: age, mean age of participants (years); BMI, mean body mass index of enrolled patients (kg/m^2); DM, diabetes mellitus; Dur, study (weeks); F%, proportion of enrolled women; Glim/met, Glimepiride/metformin; HbA1c, glycated haemoglobin at baseline (%); Ind, indication; ITCA, continuous exenatide delivering; nr, not reported; OAD, oral antidiabetic drug; OB, obesity; p-y control, patient-years in the control arm; p-y drug, patient-years in the drug arm; QD, daily administration; QWK, weekly administration.

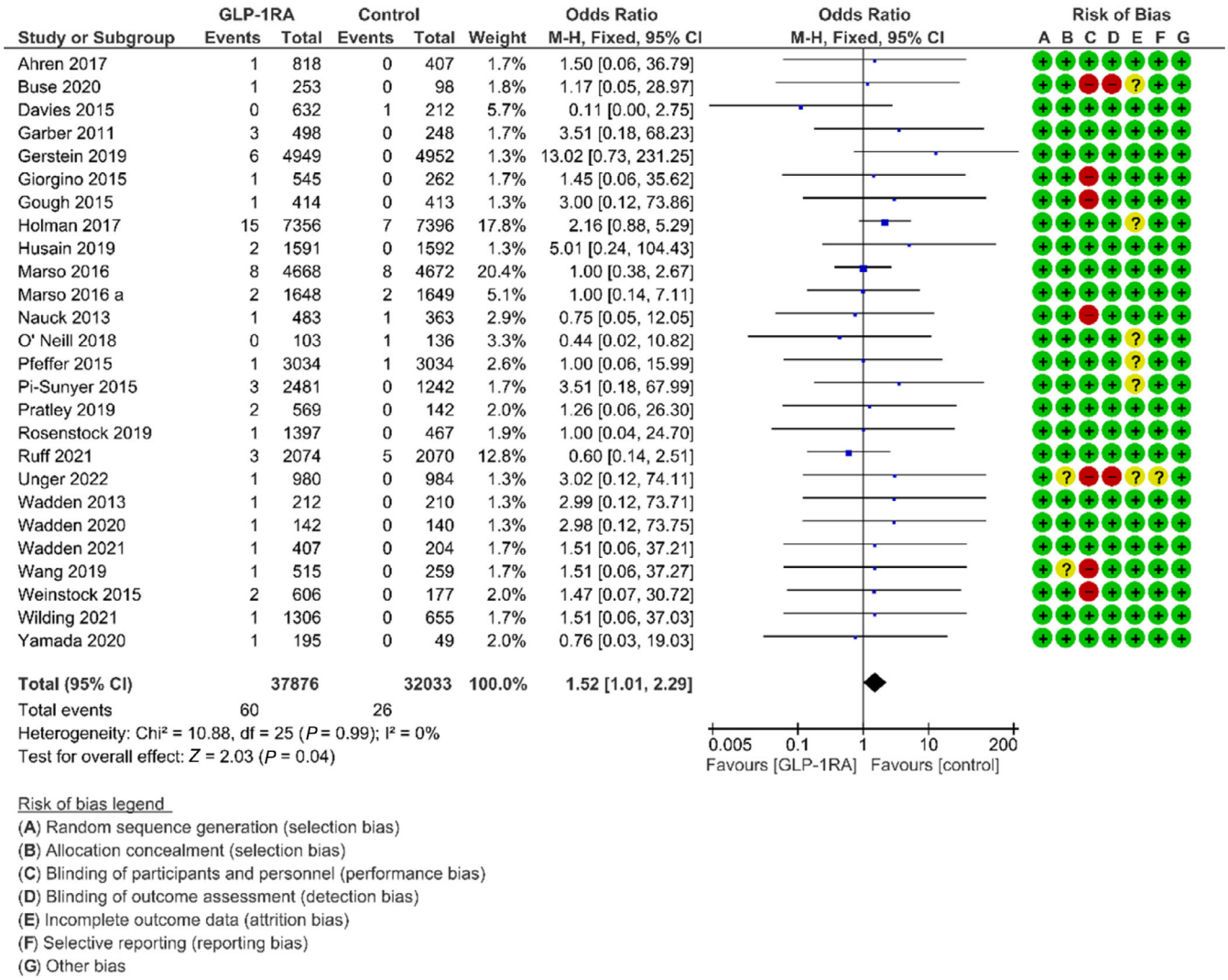

FIGURE 1 Risk of overall thyroid cancers in patients receiving glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment and in patients on comparators (forest plot). CI, confidence interval; M-H, Mantel-Haenzel.

3.3 | Subgroup analyses for overall thyroid cancer

In subgroup analyses, no difference in effect was detected between trials performed with different molecules of the class ($P = 0.77$ for difference between different molecules [Figure S7]; $P = 0.90$ when comparing human-derived and non-human-derived molecules [Figure S8]), nor was any difference detected between trials performed with different comparators ($P = 0.99$, Figure S9). In addition, no difference in effect was observed between trials designed for diabetes mellitus or obesity ($P = 0.74$ for difference between groups [Figure S10]); furthermore, no difference was found between trials enrolling more or less than 50% of women ($P = 0.62$, Figure S11), age at enrolment lower or higher than the median age (56 years; $P = 0.90$, Figure S12), or baseline BMI above or below the median value (32 kg/m^2; $P = 0.46$, Figure S13).

When analysing separately trials with different durations, the association of GLP-1RA with thyroid cancer was statistically significant only in trials of at least 104 weeks (MH-OR 1.76 [95% CI 1.00, 3.12]; $P = 0.05$ [Figure S14]), although the difference across groups of studies was not statistically significant ($P = 0.76$ [Figure S14]).

3.4 | Papillary thyroid cancer

The visual analysis of funnel plots for PTC did not suggest any risk of publication bias (Figure S15). PTCs were reported in 15 trials, overall enrolling 51 720 patients; the association with GLP-1RA treatment was not significant (MH-OR 1.54 [95% CI 0.77, 3.06]; $P = 0.22$, $I^2 = 0\%$ [Figure 2]). As an exploratory post hoc analysis, we also grouped all the thyroid cancers excluding those reported as MTCs, observing a significant effect of GLP-1RA treatment (MH-OR 1.51 [95% CI 1.00, 2.29]; $P = 0.05$, $I^2 = 0\%$ [Figure S16]).

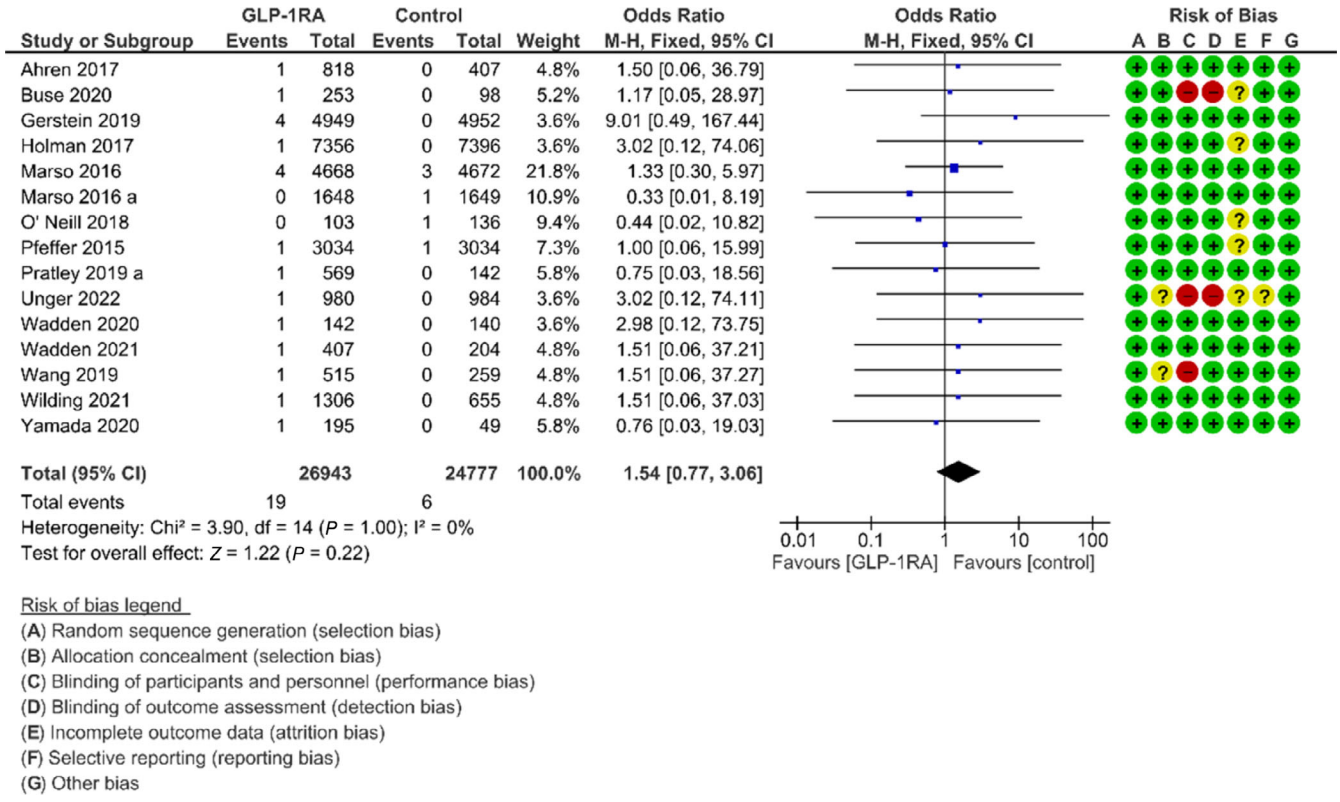

FIGURE 2 Risk of papillary thyroid cancers in patients receiving glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment and in patients on comparators (forest plot). CI, confidence interval; M-H, Mantel-Haenzel.

3.5 | Medullary thyroid cancer

Only three trials reported cases of MTC; the association between GLP-1RA treatment and MTC was not significant (MH-OR 1.44 [95% CI 0.23, 9.16]; $P = 0.55$, $I^2 = 0\%$ [Figure S17]).

4 | DISCUSSION

This meta-analysis suggests that GLP-1RA treatment may be associated with a moderate increase in risk of thyroid cancer, not dissimilar in its extent from that reported by a recent observational study,[12] which led to some methodological discussion.[21,22,56] This is, to our knowledge, the first meta-analysis of RCTs showing such results: previous meta-analyses did not find a significant effect on thyroid cancer, probably because of the lack of sufficient statistical power.[15,57–59]

The issue of the biological plausibility of the association of GLP-1RA treatment with thyroid cancer is complex. Thyroid malignancies include at least two distinct forms[60] (follicular cell-derived, of which PTC is the most common subtype, and medullary carcinoma), with different biological characteristics. Both C cells and thyrocytes express GLP-1 receptors,[17] and PTC cells express those receptors to a greater extent than normal cells.[18] However, it is unclear whether the stimulation of GLP-1 receptors is capable of inducing cell growth in thyrocytes.[18]

The statistical power of the present analysis is insufficient to establish whether the increase in overall thyroid cancer incidence was determined by MTC, PTC, or both. Notably, in epidemiological studies a significant association with GLP-1RA treatment could be detected for medullary, but not for papillary cancer.[12] On the other hand, the overall incidence of PTC is much greater than that of MTC[61]; therefore, it is likely that an increase in overall cancer incidence is determined, at least partly, by an effect on PTC. In addition, clinical trials with GLP-1RAs typically exclude patients with a personal or family history of MTC or with elevated calcitonin levels, thus selecting a population at relatively low risk for this specific malignancy.

It should also be considered that, unless MTC cases were listed as an event of special interest, the differential diagnosis of types of thyroid malignancies would not necessarily be reliable in clinical trials. A similar problem affects observational studies; the main survey attempting to discriminate MTC from PTC[12] used indirect markers of limited reliability.[21,22] In addition, since summaries of product characteristics issued by the main regulatory authorities include warnings about exercising caution in using GLP-1RAs in patients with a family or personal history of MTC, it is unlikely that observational studies will be able to discriminate in a reliable manner the potential effects of those drugs on the incidence of MTC in the future.

Some further limitations of the present meta-analysis should be considered for a correct interpretation of its results. Thyroid malignancies were not among the predefined endpoints of clinical trials,

and they were recorded only when listed as serious adverse events. Being designed for other endpoints (usually glycaemic control, weight loss, or cardiovascular outcomes), most of the trials of GLP-1RAs may have had an insufficient duration for the assessment of their effects on the development of malignancies. Notably, the effect of GLP-1-RA treatment on thyroid cancer was significant only in trials with longer duration, although the difference across groups of trials with different durations did not reach statistical significance. However, we should be aware that the inclusion of trials with relatively short duration could have diluted the results. In addition, the relatively low incidence of thyroid cancer, with many of the smaller trials having zero events in one or both treatment arms, limits the precision of the estimates of effect. The relatively small number of observed events accounts for the low fragility index, indicating that further trials could modify the present results. In this regard, the FDA has prompted the design of additional studies in animals and the establishment of a cancer registry to monitor the annual incidence of thyroid cancer over 15 years, a more reliable time frame to study malignancies with a low incidence.[62]

A further limitation is the specificity of case mix: the population enrolled in clinical trials is not fully representative of those receiving treatment in routine clinical practice; in particular, study protocols of most trials exclude patients at higher risk of MTC. Furthermore, it was not possible to retrieve data from one large trial with liraglutide,[29] although the analysis of funnel plots did not suggest selective reporting.

This study nevertheless has several strengths. The use of clinical trials in which the allocation to different treatments is determined by randomization allows patients receiving GLP-1RAs to be compared with controls. This overcomes the main limitation of observational studies, the results of which can be affected by uncontrolled (or inadequately controlled) confounders; in the case of GLP-1RAs, the relatively high proportion of obese patients among those receiving treatment could produce a bias, since excess weight is a risk factor for thyroid malignancies.[22,63] However, in the present meta-analyses no differences could be detected between subgroups of trials with different mean BMI at enrolment. A further strength is the low heterogeneity of results, suggesting that the observed association of GLP-1RA treatment with thyroid cancer is independent of trial characteristics and case mix.

Although the results are far from conclusive, the combined analysis of available randomized trials confirms a clear safety signal, suggesting a possible association of GLP-1RA with a moderate increase in the risk of thyroid cancer. The actual clinical impact of this association is limited by the relatively low incidence of thyroid cancer in the general population. Indeed, the estimated NNH, as calculated using data from clinical trials, is well above 1000 patients for 5 years. Conversely, figures for the number needed to treat to prevent a major cardiovascular event among high-risk patients with diabetes are considerably smaller.[64] In patients with diabetes and in obese individuals with high cardiovascular risk, the possible effect of GLP-1RAs on thyroid cancer is largely outweighed by the demonstrated clinical benefits, and can be considered irrelevant. However, even a relatively infrequent adverse event can raise greater concern when the drug is administered to people at lower risk of comorbidities, for example, moderately overweight subjects without concurrent cardiovascular risk factors.

In conclusion, results of RCTs seem to confirm a possible moderate increase in the risk of thyroid cancer in patients treated with GLP-1RAs. Further data are needed to verify such an effect, to better assess its actual clinical relevance, and to discriminate the possible effects on different types of thyroid malignancies.

AUTHOR CONTRIBUTIONS

Giovanni Antonio Silverii, Matteo Monami, Marco Gallo and Edoardo Mannucci made the analysis plan, researched the data, performed analyses, contributed to discussion, and wrote the first draft of the manuscript. Alberto Ragni, Valerio Renzelli, Francesco Prattichizzo and Antonio Ceriello contributed to discussion and reviewed and edited the manuscript. All authors approved the final version of the manuscript. All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

Giovanni Antonio Silverii has received speaking fees and/or travel grants for scientific meetings from Abbott, Astra Zeneca, Eli-Lilly, Novo-Nordisk, Sanofi, outside the submitted work; Matteo Monami has received speaking fees from Astra Zeneca, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, outside the submitted work. The unit directed by Edoardo Mannucci has received research grants from Abbott, Eli-Lilly and Novo Nordisk, outside the submitted work. Marco Gallo has received speaking fees and/ or travel grants for scientific meetings from AAA, Astra-Zeneca, Boehringer-Ingelheim, Bruno Farm., Guidotti, Eli-Lilly, IBSA, Lifescan, MSD, Mundipharma, Novo Nordisk and Sanofi, and served on scientific advisory panels for Boehringer-Ingelheim, MSD and Novo Nordisk, outside the submitted work. Valerio Renzelli has received travel grants for scientific meetings from Androlabs, outside the submitted work. Francesco Prattichizzo is a lecturer for BERLIN-CHEMIE, outside the submitted work. Alberto Ragni has received travel grants for scientific meetings from IBSA, outside the submitted work; Antonio Ceriello is on the advisory board and does consultancy and lectures for AstraZeneca, BERLIN-CHEMIE, Eli Lilly, Novo Nordisk, Mitsubishi, Roche Diagnostics and Theras Lifetech, outside the submitted work. Edoardo Mannucci has received consultancy fees from Merck and Novartis, speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis, outside the submitted work.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15382.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

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