RESPONSE TO COMMENT ON BEZIN ET AL.

GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Diabetes Care 2023;46:384–390

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We read with great interest the comments by Endo et al. (1), Mañas-Martinez and Gimeno-Orna (2), and Smits and van Raalte (3) on our article (4). They underline several limitations to our study, most of which had been discussed already in the article (4) and very clearly presented in the commentary by Thompson and Stürmer (5).

We deeply agree with the comments raised in the commentary and most of the interrogations expressed in the comments. Here, we take the opportunity to further discuss these and try to enrich the discussion.

First, both Endo et al. (1) and Mañas-Martinez and Gimeno-Orna (2) raised the question of the potential residual confounding associated with BMI, with obesity being more prevalent in case subjects than in control subjects and more likely to drive the prescription of glucagon-like peptide 1 receptor agonists (GLP-1 RA). We initially did not consider this variable for adjustment, as obesity is very imperfectly captured within the French National Health Data System (SNDS) database (few reimbursed drugs and little hospital billing information related to obesity). However, we performed additional analyses to test how adjustments based on the information we had would affect the results. In doing so, the adjusted hazard ratio for exposure to GLP-1 RA and the risk of thyroid cancer were estimated at 1.55 (95% CI 1.25–1.92) for 1–3 years of cumulative use and 1.33 (95% CI 1.03–1.72) for cumulative use exceeding 3 years, very close to the values presented in the publication.

Second, the question of potential residual confounding was also raised regarding the higher prevalence at baseline of thyroid diseases and thus potentially higher use of radioactive iodine therapy (noted by Endo et al. [1]) or the higher use of several cardiovascular medications (noted by Smits and van Raalte [3]) in some cases. We certainly did not include those in our analyses, and other factors might be discussed as well. The risk of residual confounding, even though difficult to fully discard, is limited here by the likelihood that these characteristics also are determinants of the prescription of GLP-1 RA. We did not find evidence that an association between radioactive iodine therapy and an increased risk of GLP-1 RA prescription was ever suspected, for instance. In the absence of this association, confounding cannot happen. To better answer Smits and van Raalte (3), who provided crude association estimates for several cardiovascular medication classes in case subjects, we performed an E-value computation. E-value is a measure representing the strength of association a potential unconsidered confounder would need to have with both the event and exposure of interest to fully explain away a specific treatment–outcome association (6). Here, it was estimated to be at least 1.99 (for the association to >3 years of GLP-1 RA use), far exceeding the estimates for association provided for any of the cardiovascular medications.

Third, Smits and van Raalte (3) made additional comments. They first asked us to provide risk for exposure time on a linear scale. This would have been of great interest, and we do agree that the categories of accumulated exposure we could use are insufficient to fully investigate a dose-dependent or duration-dependent association. Figures for exposed patients unfortunately are too limited to allow going further and responding to the request of Smits and van Raalte (3). They also commented on the limitations of pharmacovigilance disproportionality analysis and especially notoriety bias. We are fully aware of these issues (7); their existence is one of the very reasons the analysis we presented constituted a secondary analysis. Even if such an analysis can provide additional information, it should never be considered an alternative to pharmacoepidemiology studies. They present with outstanding performance for signal detection but do not provide reliable estimates of risks.

Fourth, Endo et al. (1) commented on the limitation our study presented for the identification of medullar cancers in the absence of anatomopathological information, even after considering a diagnosis of thyroid cancer associated with dosing of serum calcitonin and carcinoembryonic antigen. We fully agree with their comment and discussed this topic in our article.

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Finally, there was a last comment by Goldenberg and Jain (8). It quite surprised us, as both the tone and content are mostly unhelpful. In terms of content, it first shows misunderstandings of pharmacoepidemiological concepts we cannot discuss in detail here. We can only reassure the authors by confirming that, as written in the article, patients with a history of cancer (including thyroid cancer) were excluded from the initial cohort. Their comment also shows the limits of critically appraising meta-analysis publications. As a contradiction to our results, Goldenberg and Jain (8) cite the recent meta-analysis by Hu et al. (9), arguing that they reported neutral results for the association between GLP-1 RA and thyroid cancer (risk ratio 1.30; 95% CI 0.86–1.97). In contrast to the opinion of Goldenberg and Jain (8), these results are actually quite consistent with ours. First, the estimate reported is very close to ours and is not neutral. Second, nonsignificant results (if this is what Goldenberg and Jain [8] consider "neutral") cannot be retained here, and the meta-analysis by Hu et al. (9) should be considered inconclusive. As it relied on a very limited number of cases (n = 92), it was undersized, with a power that can be estimated at less than 35%. Had it been large enough but presented with the very same incidences, it is quite likely that the meta-analysis by Hu et al. (9) would have reached the same conclusion as we did.

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References

1. Endo M, Roth MY, Tylee TS, DeSantis A, Hirsch IB. Comment on Bezin et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384–390 (Letter). Diabetes Care 2023;46:e118. DOI: 10.2337/DC22-2454

2. Mañas-Martinez AB, Gimeno-Orna JA. Comment on Bezin et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384–390 (Letter). Diabetes Care 2023;46:e119

3. Smits MM, van Raalte DH. Comment on Bezin et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384–390 (Letter). Diabetes Care 2023;46:e120

4. Bezin J, Gouverneur A, Pénichon M, et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384–390

5. Thompson CA, Stürmer T. Putting GLP-1 RAs and thyroid cancer in context: additional evidence and remaining doubts. Diabetes Care 2023;46:249–251

6. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–274

7. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 2007;30:891–898

8. Goldenberg RM, Jain AB. Comment on Bezin et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384–390 (Letter). Diabetes Care 2023;46:e117

9. Hu W, Song R, Cheng R, et al. Use of GLP-1 receptor agonists and occurrence of thyroid disorders: a meta-analysis of randomized controlled trials. Front Endocrinol 2022;13:927859