Increased risk of hypereosinophilia following initiation of glucagon-like peptide 1 receptor agonist: A symmetry analysis using the Danish health registries

Glucagon-like peptide 1 receptor agonists (GLP1-RA) are increasingly used in the treatment of Type 2 diabetes and as antiobesity drugs. Cases of hyper-eosinophilic syndrome (HES) following initiation of GLP1-RA have been reported [1]. HES is defined by eosinophil counts of $1.5 \times 10^9/L$ or greater and related end-organ damage [2]. Because these events are too rare to be detected in randomized controlled trials, we aimed to quantify the association between GLP1-RA initiation and incident hypereosinophilia (HE) using real-world data.

Leveraging nationwide Danish prescription [3] and laboratory data [4], we conducted a sequence symmetry analysis (SSA) investigating the occurrence of HE following initiation of GLP1-RA and for comparison sodium–glucose co-transporter 2 inhibitors (SGLT2i) and dipeptidyl peptidase 4 inhibitors (DPP4i) [5].

The SSA compares the occurrence of HE during a symmetric time window before and after initiation of the drug of interest. If there is no association between drug initiation and HE, we would expect HE to occur equally often during both windows. However, if GLP1-RA use increases eosinophil counts, we would expect HE to occur more frequently after initiation. The sequence ratio (SR) is calculated as the number of HE events after drug initiation divided by the number of HE events before drug initiation and corresponds to the incidence rate ratio obtained in the corresponding cohort study [6]. If the rate of HE is increased after initiation of GLP1-RA compared to the period before initiation, we would expect an SR above 1.
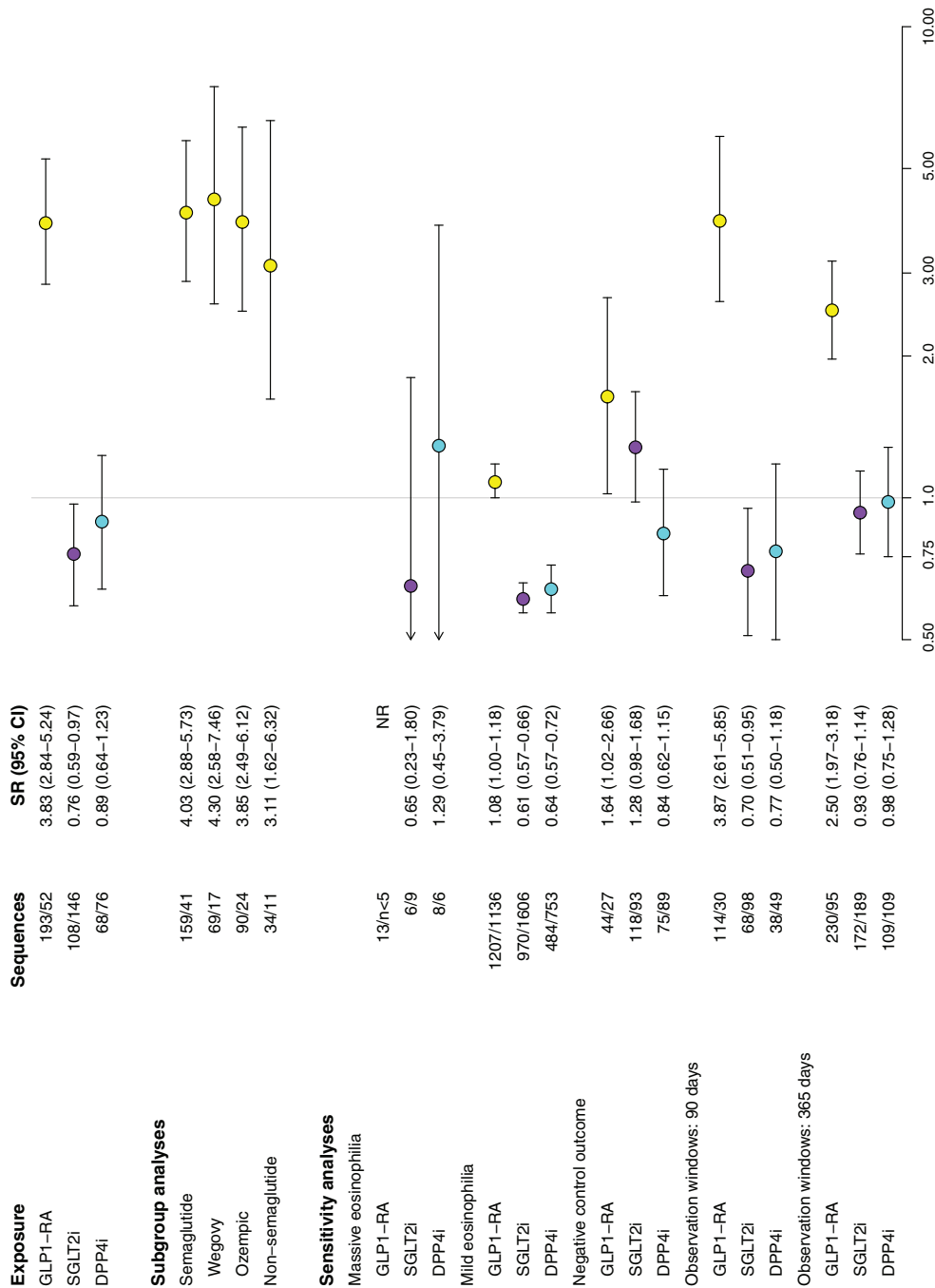
We identified all individuals who initiated a GLP1-RA, SGLT2i or DPP4i (Appendix) between 1 June 2015 and 31 May 2024 and obtained eosinophil counts of $1.5 \times 10^9/L$ or greater within the last 180 days before the drug initiation, or within the first 180 days after. Observed SRs were adjusted

for temporal trends in HE [5]. In subgroup analyses, we evaluated semaglutide and other GLP1-RAs separately, as well as Ozempic and Wegovy. For sensitivity analyses, we calculated SRs for observation windows of 90 and 365 days and with mild ($\geq 0.5–1.5 \times 10^9/L$) and massive eosinophilia ($\geq 5 \times 10^9/L$) as outcomes. Finally, we used a thrombocyte count below $50 \times 10^9/L$ as a negative control outcome.

The study was approved by the institutional data protection board at the University of Southern Denmark and the Danish Health Data Authority (Project number FSEID-00006047). Ethical approval is not needed in Denmark for studies based purely on registry data.

We identified 213,521 individuals who initiated a GLP1-RA among whom 245 had HE within 1 year of drug initiation. The median age was 54 years (interquartile range [IQR] 42–63), 49% were female and median year of initiation of GLP1-RA was 2022 (IQR 2021–2023). Of these, 193 individuals had HE after drug initiation, and 52 individuals had HE before drug initiation, yielding an SR of 3.83 (95% confidence interval [CI] 2.84–5.24). Among initiators of SGLT2i and DPP4i, we found SRs of 0.76 ($N = 108/146$, CI 0.59–0.97) and 0.89 ($N = 68/76$, CI 0.64–1.23).

In subgroup analyses, SRs for semaglutide, other GLP1-RAs, Wegovy and Ozempic were similar to results for all GLP1-RAs combined (Fig. 1). The outcome mild eosinophilia yielded an SR of 1.08 for GLP1-RA initiators ($N = 1207/1136$, CI 1.0–1.18). For massive eosinophilia, we observed 13 events after GLP1-RA initiation and less than 5 events before initiation. Analyses with shorter and longer observation windows yielded elevated SRs (SR 3.87, CI 2.62–5.85 and 2.50 [1.97–3.18]). For the negative-control outcomes, we found for GLP1-RA, SGLT2i and DPP4i, respectively, SRs of 1.64 ($N = 44/27$, CI 1.02–2.66), SR of 1.28 ($N = 118/93$,

Exposure	Sequences	SR (95% CI)
GLP1–RA	193/52	3.83 (2.84–5.24)
SGLT2i	108/146	0.76 (0.59–0.97)
DPP4i	68/76	0.89 (0.64–1.23)
Subgroup analyses		
Semaglutide	159/41	4.03 (2.88–5.73)
Wegovy	69/17	4.30 (2.58–7.46)
Ozempic	90/24	3.85 (2.49–6.12)
Non-semaglutide	34/11	3.11 (1.62–6.32)
Sensitivity analyses		
Massive eosinophilia		
GLP1–RA	13/n–5	NR
SGLT2i	6/9	0.65 (0.23–1.80)
DPP4i	8/6	1.29 (0.45–3.79)
Mild eosinophilia		
GLP1–RA	1207/1136	1.08 (1.00–1.18)
SGLT2i	970/1606	0.61 (0.57–0.66)
DPP4i	484/753	0.64 (0.57–0.72)
Negative control outcome		
GLP1–RA	44/27	1.64 (1.02–2.66)
SGLT2i	118/93	1.28 (0.98–1.68)
DPP4i	75/89	0.84 (0.62–1.15)
Observation windows: 90 days		
GLP1–RA	114/30	3.87 (2.61–5.85)
SGLT2i	68/98	0.70 (0.51–0.95)
DPP4i	38/49	0.77 (0.50–1.18)
Observation windows: 365 days		
GLP1–RA	230/95	2.50 (1.97–3.18)
SGLT2i	172/189	0.93 (0.76–1.14)
DPP4i	109/109	0.98 (0.75–1.28)

Fig. 1 *Number of hypereosinophilia events before and after drug initiation and sequence ratios with 95% confidence intervals for main, subgroup and sensitivity analyses, and corresponding forest plot. Exposure drugs with the corresponding number of sequences, sequence ratios and confidence intervals are presented. The outcome is an eosinophil count greater than $1.5 \times 10^9/L$, except in sensitivity analyses of massive eosinophilia, mild eosinophilia and the negative control outcome, where the outcomes are, respectively, an eosinophil count greater than $5 \times 10^9/L$, an eosinophil count of ≥ 0.5–$1.5 \times 10^9/L$ and an incident thrombocyte count below $50 \times 10^9/L$. The corresponding sequence ratios are displayed in a forest plot on the right-hand side. Yellow dots represent glucagon-like peptide 1 receptor agonists (GLP1-RAs), purple dots represent sodium–glucose co-transporter 2 inhibitors (SGLT2i), and light blue dots represent dipeptidyl peptidase 4 inhibitors (DPP4i). Note: Incident thrombocyte count below $50 \times 10^9/L$. CI, confidence interval; NR, not reported (according to Danish law, counts below 5 cannot be reported); SR, sequence ratio.*

CI 0.98–1.68) and SR of 0.84 (N = 75/89, CI 0.62–1.15) after initiation. **Fig**. **S1** shows a steep increase in HE during the first 3 months after GLP1-RA initiation, which was not observed for SGLT2i or DPP4i initiators.

In this nationwide study, we found that HE is three times more likely to occur after initiation of GLP1-RAs compared to the period prior to initiation. This finding was specific to GLP1-RAs and not observed for other antidiabetic drugs. Albeit the negative control outcome generated a result that was non-null for GLP1-RAs, results for the negative control outcome were much closer to 1.0 compared to the main analysis and were compatible with the results for SGLT2i. Thus, our study provides evidence of a temporal association between the initiation of GLP1-RAs and HE. The main limitation of our study is that the outcome was biochemically defined HE and not end-organ damage due to HE. Another important limitation is that the study population only included individuals who initiated GLP1-RA and had an eosinophil count measured. Larger studies are needed to quantify the potential association between GLP1-RAs and clinically manifest HES.

The data underlying this article cannot be shared publicly due to Danish privacy regulations. Danish data are available to authorized researchers after application to the Danish Health Data Authority (https://sundhedsdatastyrelsen.dk).

The analytical source code can be obtained from https://gitlab.sdu.dk/lclund/glp1-hes/. A protocol was registered prior to data analysis and is available at https://osf.io/sabzk.

Author contributions

Martin Torp Rahbek and Lars Christian Lund had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Lars Christian Lund, Martin Torp Rahbek, Anton Pottegård, Jesper Hallas and Kasper Bruun Kristensen conceptualized the study. Søren Andreas Just and Hussam Mahmoud Sheta provided important input to the methodology and interpretation. Lars Christian Lund performed the data analysis. Martin Torp Rahbek drafted the original manuscript, and all authors critically revised the manuscript and approved the final version for publication. Martin Torp Rahbek attests that Anton Pottegård, Jesper Hallas, Lars Christian Lund, Søren Andreas Just, Kasper Bruun Kristensen and Hussam Mahmoud Sheta meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

The data underlying this article cannot be shared publicly due to Danish privacy regulations. Danish data are available to authorized researchers after application to the Danish health data authority (https://sundhedsdatastyrelsen.dk). The analytical source code can be obtained from https://gitlab.sdu.dk/lclund/glp1-hes/. A protocol was registered prior to data analysis and is available at https://osf.io/sabzk

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix Table 1. ATC-codes used to identify exposures, negative controls and outcomes in the Danish National Prescription Registry.

Supplementary Figure 1. Number of hypereosinophilia events during the six months before and after initiation of GLP1-RA, SGLT2i or DPP4i. Supplementary figure 1: Temporal distribution of hyper eosinophilia relative to initiation of GLP1-RA, SGLT2i, or DPP4i, respectively. The dashed line represents the date of initiation of GLP1-RA, SGLT2i, or DPP4i. Dark blue segments represent the number of hypereosinophilia events prior to initiation, while light grey segments represent HE events after initiation. x-axis: months before and after the prescription date; y-axis, hyper eosinophilia (N). ■