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Association between various dosage forms of semaglutide and ocular adverse events in a real-world setting

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Abstract

Background This study systematically compares the risk of long-term ocular adverse events between subcutaneous and oral semaglutide preparations to assess pathway-specific safety differences.

Methods In this study, the Report odds ratio (ROR) technique was employed to detect signals of adverse drug reactions (ADRs) associated with the use of semaglutide. Analysis was conducted on data extracted from the FDA Adverse Event Reporting System (FAERS) database, covering the period from 2004(Q1) through 2024(Q3). This investigation encompasses a descriptive analysis focused on the administration of semaglutide through various routes, encompassing a broad range of demographics including gender (male and female), age groups, along with other demographic data and the timing of disease onset. Following this, the study employs the ROR methodology to assess the differential adverse event signals across distinct semaglutide formulations.

Results We categorized the eye as the System Organ Class (SOC) and obtained 1733 ADE reports related to it from the FAERS database. Of these, 1541 reports were associated with injectables, while tablets were linked to 192 ADE reports. In both dosage forms, most cases occurred within the first month of administration, although the median time to onset (TTO) differed, with injectables identified at 7.00 [IQR 0.00-56.00] days and tablets at only 3.50 [IQR 0.00-35.00] days. It is worth noting that 5.41% of patients administered subcutaneous injections and 2.17% of those receiving oral medications reported ADEs following one year of treatment with semaglutide. Furthermore, female patients exhibited a higher susceptibility to ocular adverse reactions compared to their male counterparts. Regarding the primary preferred terms (PTs), blurred vision constitutes 34.33% of the total ADEs associated with tablet formulations. This incidence is marginally higher than that observed with injectable formulations. This investigation further discerned ocular ADEs signals associated with specific formulations: subcutaneous injections have a higher frequency of reports concerning retinal complications, such as diabetic retinopathy, ischemic optic neuropathy, retinal detachment, retinal tear, and retinal hemorrhage.

Conclusion The results of this study identified a significant difference between subcutaneous and oral semaglutide in ocular ADE risk, providing some evidence for dosage form selection and risk monitoring for clinical use.

Keywords Different administration routes, Semaglutide, Eye disorders, Safety analysis

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Introduction

As a long-acting glucagon-like peptide- 1 receptor agonist (GLP- 1Ra), semaglutide effectively regulates blood sugar levels by enhancing insulin secretion in a glucose-dependent manner and suppressing glucagon production [1, 2]. Current evidence indicates that semaglutide has a dual profile concerning ocular safety: it appears not to be associated with an increased risk of non-arteritic anterior ischemic optic neuropathy (NAION) in the general population. Moreover, its potential benefits in glycemic control and cardiovascular health may outweigh any potential risks [3]. On the other hand, factors such as direct drug toxicity, abnormal vascular regulation, or blood glucose fluctuations may induce acute optic nerve injury such as NAION [4]. From the perspective of molecular pathology, the potential development of ocular diseases due to long-term use of semaglutide could primarily be attributed to the rapid fluctuations in blood glucose levels induced by the medication. These changes can disrupt the adaptive regulation of oxygenation in the retinal blood vessels, inhibit angiogenesis, and lead to further deterioration of the already compromised vascular endothelium in hyperglycemic conditions, potentially accelerating the progression of existing diabetic retinopathy [5–8]. This rapid change in blood glucose levels may also lead to increased retinal blood flow and stress on blood vessels, affecting ocular microcirculation. This can result in or exacerbate macular edema [9].

As of now, the US Food and Drug Administration (FDA) has approved semaglutide in the forms of a subcutaneous injection (marketed as Ozempic and Wegovy) and an oral tablet (sold under the brand name Rybelsus) for treating type 2 diabetes and obesity [10–12]. The adverse event reporting system revealed a statistically significant similarity between semaglutide-related adverse drug reactions in different dosage forms [13, 14]. However, we found significant limitations in the evidence for differences between the two dosage forms in specific ophthalmology. Initial research has predominantly concentrated on the injectable form of the drug, whereas the ocular safety of oral tablets, particularly in comparison to injectables, remains inadequately assessed. For instance, the specific risk of non-arteritic anterior ischemic optic neuropathy (NAION) linked to different dosage forms is still not well-defined. Moreover, there is an absence of extensive real-world data; some studies have suggested that the drug might hasten the progression of diabetic retinopathy, whereas others indicate no significant impact from its long-term use on retinopathy [15, 16]. This results in an insufficient quantitative evidence base for conducting risk-benefit evaluations of various dosage forms.

Considering the existing controversies and gaps in evidence, this study utilized this study utilizes real-world adverse event reports to analyze and compare the incidence, severity, and reporting patterns of ocular adverse drug events (ADEs) associated with subcutaneous and oral semaglutide. Through signal detection methods, the study identified serious retinal complications, such as non-arteritic anterior ischemic optic neuropathy (NAION) and retinal hemorrhage, that were significantly linked to specific dosage forms. This analysis aims to highlight priority warning targets for enhanced clinical monitoring.

Materials and methods

Data source

The dataset utilized for this study was sourced from the FastSignal team using FastSignal V2.0, accessible at http://www.faers.trit-bio.com. This tool draws upon the FDA Adverse Event Reporting System (FAERS), the largest drug safety database globally, which aggregates spontaneous adverse reaction reports from a broad demographic spectrum worldwide. The comprehensive and international nature of this dataset is crucial for establishing associations between pharmaceutical agents and adverse reactions. Specifically, the data employed in analyzing the safety profiles of various formulations of semaglutide were extracted from the FAERS database, spanning from 2004(Q1) to 2024(Q3).

Data processing

The specific steps include: 1) Ensure that all target drug data are extracted from the FAERS database. We used Medical Subject Headings (MeSH) with semaglutide as the target compound to eliminate duplicate cases before statistical analysis; 2) To enhance the credibility of the results, we only extracted reports of adverse events where the target drug was considered to cause a PS role; 3) We categorized the obtained data into oral and injectable forms for distinction; 4) Utilizing the Medical Dictionary for Regular Activities (MedDRA), version 27.0, we identified each individual report at the SOC, the PT, and Standardized MedDRA Query (SMQ) levels. Comparative analyses were conducted using disproportionality analysis and reporting odds ratio methods. Figure 1 provides a detailed overview of the multi-step process of data mining, cleansing, and analysis.

Signal detection

In the realm of ADE signal detection, prevalent methodologies include the ROR and the Proportional Reporting Ratio (PRR). The latter frequently employs the lower limit of the confidence interval (CI) of the PRR for signal detection. The findings from the lower CI method of

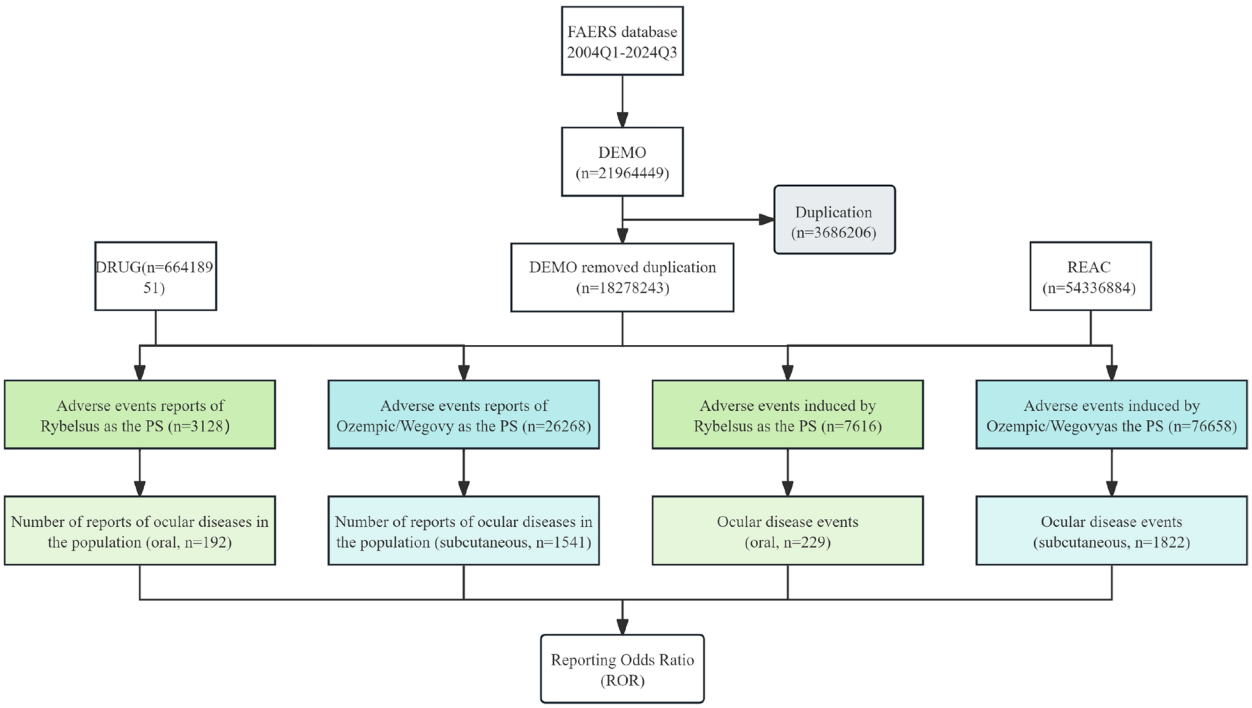

Fig. 1 The process of searching for and categorizing adverse events related to different formulations of semaglutide in the FDA's Adverse Event Reporting System (FAERS)

the PRR are generally in agreement with those obtained using the ROR method. This approach typically utilizes the threshold defined by the Medicines and Healthcare Products Regulatory Agency (MHRA) composite standard for signal identification. Although the MHRA composite standard also relies on PRR, it adopts different threshold settings compared to the conventional PRR method. Additional methodologies encompass the Bayesian Confidence Propagation Neural Network (BCPNN) and the Multi-item Gamma Poisson Shrinker (MGPS) method, detailed in Table S- 1. Each method exhibits distinct characteristics and applicability, facilitating the selection of an optimal approach to significantly enhance the precision of ADEs signal detection. In this study, we conducted an ROR analysis on unique Preferred Terms (PTs) reported for various formulations of semaglutide in the FAERS database to discern differences in ADEs signals (see Table 1). This analysis helps identify significant signals of PTs when the incidence of specific ADEs related to the target drug surpasses the background frequency, labeling the target drug is positively associated with suspected ADEs.

Comparative analysis

This analysis focuses on patients who have been included and treated with the target medication(Rybelsus, Wegovy and/or Ozempic). Statistical descriptions are conducted on a per-patient basis, meaning if a patient experiences multiple adverse events, it is only counted once. The study included a range of variables, including gender and age group, identity of the reporter (whether physician, pharmacist or patient self-reported), reporting year and country, and TTO.

Table 1 Two-by-two contingency table for disproportionality analysis

	Number of target adverse events reports	Number of other adverse events reports	Total
Target drug	a	b	a+b
Other drugs	c	d	c+d
Total	a+c	b+d	N=a+b+c+d

Results

Descriptive results

After removing duplicate entries, from 2004 (Q1) to 2024 (Q3), the FAERS database received a total of 21,964,449 semaglutide-related ADE reports, from which 1,733 reports related to ocular adverse events were further identified and organized. In Table 2, The majority of the adverse drug reaction case reports originate from the USA, followed by Denmark, the UK, and Canada. The

Table 2 Summary of basic data of ADEs of Smegallutide

Characteristics	Faers n	Number of subcutaneous cases	Number of oral cases
Total number of cases	1733	1541(88.92)	192(11.08)
Sex			
Female(%)	1087(62.72)	977(63.40)	110(57.29)
Male(%)	580(33.47)	508(32.97)	72(37.50)
Not Specified(%)	66(3.81)	56(3.63)	10(5.21)
Age			
18(%)	0(0.00)	0(0.00)	0(0.00)
18–44(%)	78(4.50)	74(4.80)	4(2.08)
45–64(%)	383(22.10)	337(21.87)	46(23.96)
65–74(%)	312(18.00)	277(17.98)	35(18.23)
⩾75(%)	132(7.62)	119(7.72)	13(6.77)
NotSpecified(%)	828(47.78)	734(47.63)	94(48.96)
Year			
2018(%)	35(2.02)	35(2.27)	0(0.00)
2019(%)	115(6.64)	115(7.46)	0(0.00)
2020(%)	170(9.81)	156(10.12)	14(7.29)
2021(%)	208(12.00)	160(10.38)	48(25.00)
2022(%)	308(17.77)	253(16.42)	55(28.65)
2023(%)	333(19.22)	299(19.40)	34(17.71)
2024(%)	564(32.54)	523(33.94)	41(21.35)
Reporter			
Consumer(%)	1193(68.84)	1097(71.19)	96(50.00)
Not Specified(%)	1(0.06)	1(0.06)	0(0.00)
Other health-professional(%)	28(1.62)	28(1.82)	0(0.00)
Pharmacist(%)	210(12.12)	161(10.45)	49(25.52)
Physician(%)	301(17.37)	254(16.48)	47(24.48)
Country			
USA(%)	1584(91.40)	1421(92.21)	163(84.90)
United Kiongdom(%)	16(0.92)	9(0.58)	7(3.65)
Denmark(%)	24(1.38)	24(1.56)	0(0.00)
Canada(%)	16(0.92)	16(1.04)	0(0.00)
France(%)	13(0.75)	13(0.84)	0(0.00)
Japan(%)	6(0.35)	0(0.00)	6(3.13)
Netherlands(%)	2(0.12)	0(0.00)	2(1.04)
Latvia(%)	2(0.12)	0(0.00)	2(1.04)

data from these regions mainly come from self-reports by local consumers. The number of reports typically increases over time. In the FAERS database regarding age, the highest number of adverse event reports without recorded age is 828, accounting for 47.78% of the total reports. The absence of this information may affect the completeness and accuracy of the data. Secondly, the number of adverse reactions reported by the 45–64 age group was 383, accounting for 22.10% of the total reports. It is noteworthy that there are no reports of ADEs related to patients under the age of 18. It is noteworthy that semaglutide-related ocular ADEs are more common in females than in males, accounting for 62.72% and 33.47% of the total cases, respectively.

Comparison of ocular adverse events reported in oral and subcutaneous administrations

General characteristics

We attempted to analyze the potential differences in adverse reactions associated with two different routes of administration. Based on the data extracted from 1733 reports in the aforementioned tables, we identified 192 adverse event reports related to the eyes for Rybelsus, comprising 229 instances of adverse events. Similarly, we

obtained 1541 adverse event reports related to the eyes for Ozempic and/or Wegovy, including 1822 instances of adverse events.

Report situation. Regarding the reports of ADEs associated with subcutaneous administration, the number has shown an increasing trend annually from the start to the end of the study period. In contrast, the number of ADEs reports for oral administration has remained stable, with its maximum sample size significantly lower than that for subcutaneous administration (oral: 55 cases vs. subcutaneous: 523 cases), this is shown in Fig. 2a. Regarding the reporting countries, there are differences between the two formulations, but both the United States and the United Kingdom have reported adverse reactions for both forms. In the United States, the volume of reports submitted is the highest (oral 81.25% VS subcutaneous 89.88%). In medical institutions, the majority of ADEs reports submitted by doctors are related to subcutaneous injections, accounting for 16.48%; whereas pharmacists predominantly report

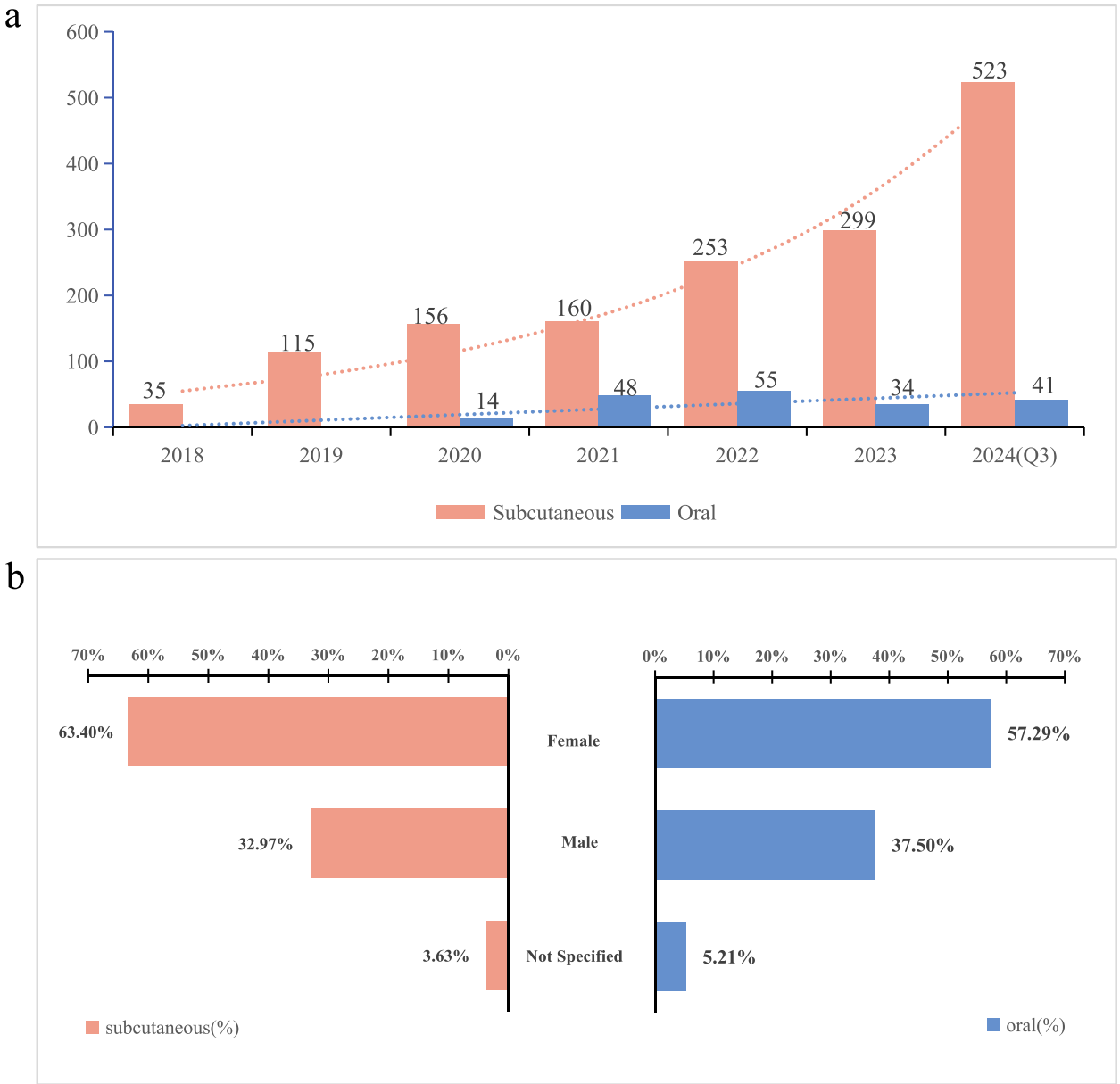

Fig. 2 Year and gender of target drug ocular related ADEs reported. **a** Distribution of ADEs of Target drug from 2018 to the third quarter of 2024 (2024 Q3). **b** Sex-and Figure age-related adverse effects at different routes of administration

incidents related to oral medications, making up 25.52% of the reports.

Gender and age. In studies that meticulously record the gender of participants, we found that females (subcutaneous 63.40%, oral 57.29%) are more likely to suffer from eye-related adverse reactions compared to males (subcutaneous 32.97%, oral 37.50%), regardless of the drug formulation. Specifically, the likelihood of female patients developing eye conditions after using the medication is nearly twice that of male patients. Among participants with specified ages, the majority are concentrated in the 45–64 age group (oral 23.96% VS subcutaneous 21.87%), followed by the 65–74 age group (oral 18.23% VS subcutaneous 17.98%), with a median age of 64 years. No reports of ADEs were observed in patients under the age of 18, as detailed in Fig. 2b.

Onset time of events. After excluding inaccurate, missing, or unknown onset reports, a total of 333 and 46 cases of ADEs were collected for injections and tablets, respectively. The median time to onset (TTO) for the injections and tablets was determined to be 7.00 [IQR 0.00 - 56.00] days and 3.50 [IQR 0.00 - 35.00] days, respectively. As shown in Fig. 3, the majority of cases occurred within the first month of administration, with 218 cases (65.47%) for subcutaneous injections and 33 cases (71.74%) for oral administration. Over time, there were 27 cases (8.11%) of ADEs occurring within 31–60 days and 5 cases (10.87%) within 61–90 days, 14 cases (4.20%) and 3 cases (6.52%) respectively. Between 91–180 days, ADEs were reported only for subcutaneous administration, with no events reported for oral administration. Notably, ADEs may still occur after one year of treatment with semaglutide, with 5.41% of subcutaneous injection cases and 2.17% of oral cases still experiencing adverse events.

Degree of disease and outcome. Within the same formulations, the probabilities of experiencing serious and non-serious adverse drug reactions (ADEs) are roughly similar. For the oral formulation, the incidence rates of adverse reactions are 46.35% for serious and 53.65% for non-serious; for the subcutaneous injection formulation, the rates are 47.57% for serious and 52.43% for non-serious. Regarding the outcomes of adverse drug reactions, the most commonly reported were other serious medical events (OT), with oral formulations accounting for 43.23% and subcutaneous injections accounting for 41.66%; followed by hospitalization (HO), where oral formulations accounted for 5.21% and subcutaneous injections accounted for 6.55%. Notably, in the reports, there was one case (0.06%) of congenital anomalies and seven cases (0.45%) of patient deaths associated with subcutaneous injection, while no such incidents were reported with the oral formulation.

Results of signal calculation for ADEs

Ranking results of signals related to eye diseases. Table 3 presents the top 30 PTs with the highest incidence of semaglutide-related ADEs for each dosage form, summarizing data from 1,613 cases of subcutaneous injections and 201 cases of oral formulations. Notably, serious outcomes such as blindness were reported in 4.98% of all Rybelsus (oral form) cases and 4.28% of Wegovy and/or Ozempic (injectable forms) cases. For ocular ADEs, blurred vision in patients using Rybelsus constituted 34.33% of the total ADEs, which was marginally higher than that observed with the injectable forms Wegovy

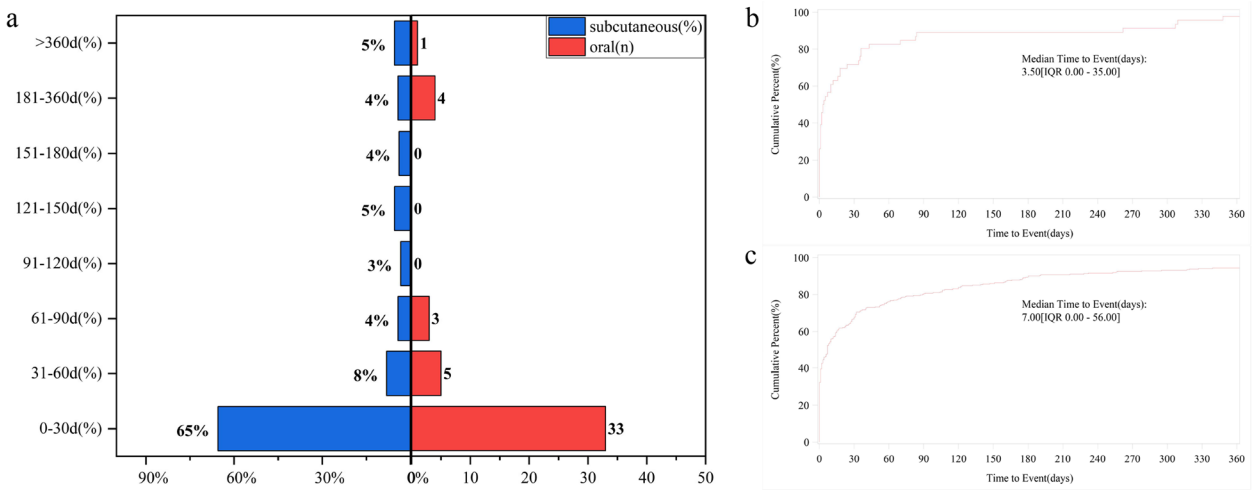

Fig. 3 Time to onset of events for different dosage forms. **a** Induction times for adverse reactions under different routes of administration. **b** Line chart of the start time of oral target drug events. **c** Line chart of the start time of the subcutaneous of the target drug event

Table 3 Disproportionality analysis

Oral			Subcutaneous		
PTs	**N(%)**	**ROR (95%CI)**	**PTs**	**N(%)**	**ROR (95%CI)**
Vision blurred	69(34.33)	4.15(3.27–5.25)	Vision blurred	433(26.84)	2.58(2.35–2.84)
Visual impairment	38(18.91)	2.45(1.78–3.37)	Visual impairment	392(24.30)	2.51(2.27–2.78)
Blindness	10(4.98)	2.03(1.09–3.78)	Cataract	98(6.08)	1.37(1.12–1.67)
Diabetic retinopathy	8(3.98)	18.99(9.49–38.02)	Diabetic retinopathy	76(4.71)	18.31(14.58–23.00)
Eye haemorrhage	6(2.99)	3.55(1.60–7.92)	Blindness	69(4.28)	1.39(1.10–1.76)
Dry eye	6(2.99)	1.12(0.50–2.50)	Retinopathy	56(3.47)	11.93(9.16–15.54)
Blindness unilateral	5(2.49)	2.88(1.20–6.93)	Eye pain	37(2.29)	0.57(0.41–0.79)
Eye pain	5(2.49)	0.78(0.32–1.86)	Diplopia	36(2.23)	1.12(0.81–1.55)
Cataract	5(2.49)	0.70(0.29–1.69)	Dry eye	36(2.23)	0.67(0.48–0.93)
Diplopia	4(2.00)	1.25(0.47–3.33)	Eye haemorrhage	31(1.92)	1.83(1.28–2.60)
Vitreous haemorrhage	4(2.00)	11.70(4.39–31.21)	Blindness unilateral	30(1.86)	1.72(1.20–2.46)
Eye swelling	4(2.00)	0.88(0.33–2.35)	Ischemic neuropathy	30(1.86)	9.15(6.38–13.12)
Visual acuity reduced	3(1.49)	0.67(0.22–2.09)	Eye disorder	27(1.67)	0.67(0.46–0.98)
Ocular hyperaemia	3(1.49)	0.55(0.18–1.70)	Vitreous floaters	23(1.43)	1.95(1.29–2.93)
Vitreous floaters	3(1.49)	2.56(0.82–7.93)	Retinal detachment	20(1.24)	1.79(1.15–2.77)
Macular degeneration	3(1.49)	2.15(0.69–6.68)	Vitreous haemorrhage	19(1.18)	5.55(3.53–8.71)
Blindness transient	2(1.00)	2.20(0.55–8.79)	Eye pruritus	18(1.12)	0.49(0.31–0.77)
Visual field defect	2(1.00)	1.96(0.49–7.85)	Ocular hyperaemia	17(1.05)	0.31(0.19–0.50)
Glaucoma	2(1.00)	0.84(0.21–3.35)	Photophobia	17(1.05)	0.75(0.47–1.21)
Retinal haemorrhage	2(1.00)	2.26(0.57–9.06)	Eye swelling	17(1.05)	0.37(0.23–0.60)
Photophobia	2(1.00)	0.89(0.22–3.55)	Lacrimation increased	17(1.05)	0.48(0.30–0.77)
Vitreous detachment	2(1.00)	7.63(1.91–30.53)	Glaucoma	16(1.00)	0.67(0.41–1.09)
Retinal tear	2(1.00)	6.77(1.69–27.09)	Eye irritation	15(0.93)	0.24(0.15–0.40)
Eye disorder	2(1.00)	0.50(0.12–2.00)	Macular degeneration	13(0.81)	0.93(0.54–1.60)
Ocular discomfort	2(1.00)	1.70(0.43–6.81)	Retinal tear	13(0.81)	4.39(2.54–7.57)
Lacrimation increased	2(1.00)	0.57(0.14–2.27)	Blindness transient	12(0.74)	1.31(0.74–2.31)
Miosis	2(1.00)	2.11(0.53–8.43)	Retinal haemorrhage	12(0.74)	1.35(0.77–2.38)
Photopsia	1(0.50)	1.27(0.18–8.98)	Ocular discomfort	12(0.74)	1.01(0.58–1.79)
Accommodation disorder	1(0.50)	10.63(1.50–75.60)	Macular oedema	11(0.68)	1.60(0.89–2.90)
Myopia	1(0.50)	3.35(0.47–23.81)	Vitreous detachment	10(0.62)	3.80(2.04–7.07)

and/or Ozempic at 26.84%. Conversely, visual impairment was less frequently reported in patients receiving oral therapy (18.91%) compared to those receiving subcutaneous injections (24.30%). Figure 4a and b display the top 30 PTs with the highest proportions of semaglutide-related reports in the oral and subcutaneous markets, respectively, accompanied by ROR calculations for these signals. Among the subcutaneous PTs, the most notable included cataract (6.08%), diabetic retinopathy (4.71%), and blindness (4.28%). For oral formulations, the most significant adverse events reported were blindness (4.98%), diabetic retinopathy (3.98%), and ocular hemorrhage (2.99%). These findings highlight differential risk profiles associated with the routes of semaglutide administration.

Results of Signal Calculation Using the ROR Method. To elucidate the signal differences of Preferred Terms (PTs) across two different routes of administration, the extracted data were further analyzed using the Reporting Odds Ratio (ROR) method, as presented in Table S- 2. We identified the top 30 PTs with the highest frequency of positive signals for the target drugs in various dosage forms. A total of 1,324 cases were documented for the subcutaneous route, involving 19 PTs, whereas the oral route comprised 140 cases, involving 7 PTs. Among oral formulations, the strongest signal was observed for diabetic retinopathy (95% CI: 18.99, 9.49–38.02), followed by vitreous hemorrhage (95% CI: 11.70, 4.39–31.21). In contrast, subcutaneous administration presented a broader spectrum of reported conditions (as depicted in Fig. 5c), including retinopathy (95% CI: 11.93, 9.16–15.54), ischemic optic neuropathy (95% CI: 9.15, 6.38–13.12), diabetic ophthalmopathy (95% CI: 7.84, 2.93–21.01), diabetic retinal edema (95% CI: 6.42, 2.40–17.18), and

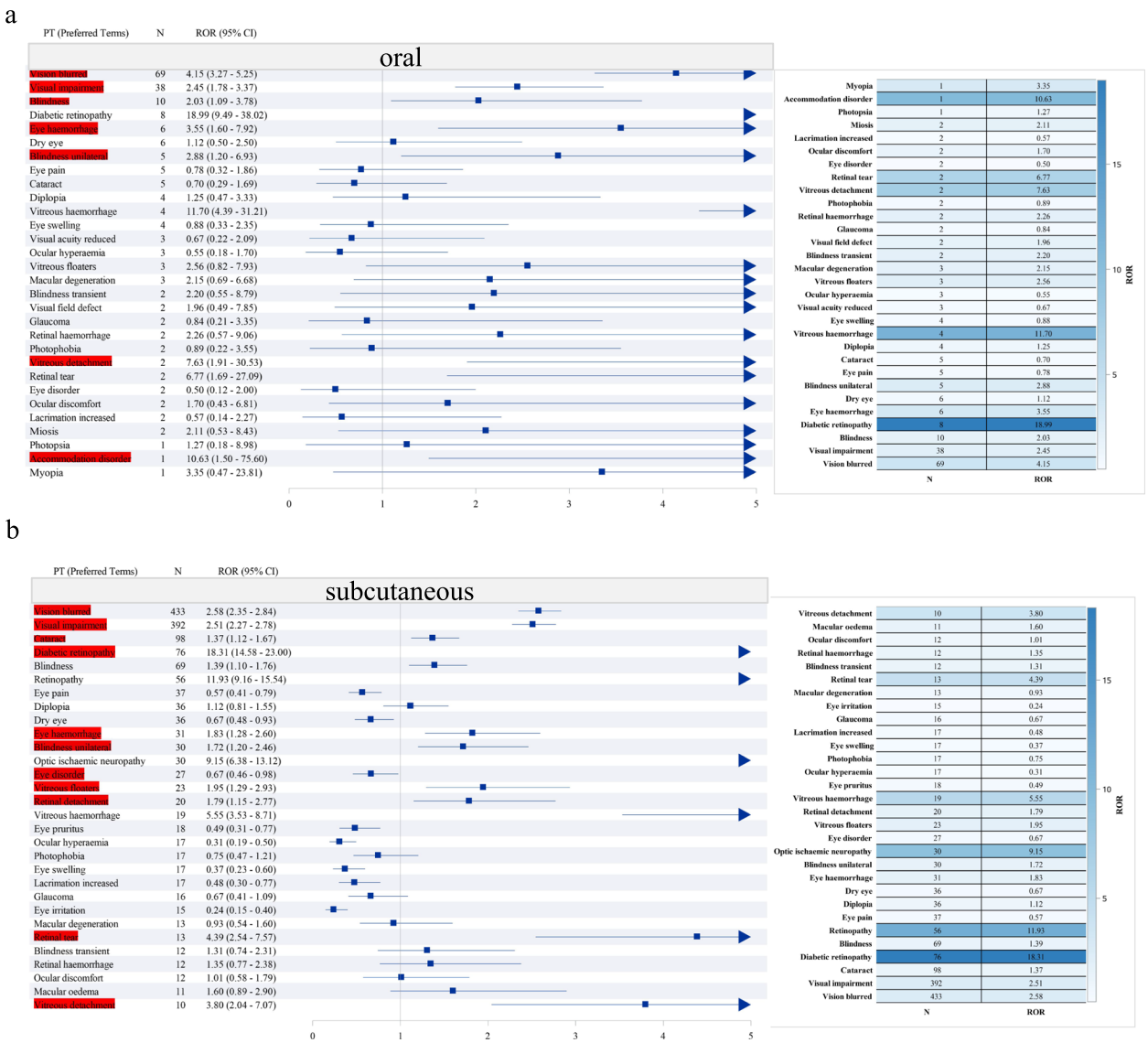

Fig. 4 PTs signaling under different routes of administration. **a** The top 30 preferred words for the positive signal intensity of oral target drugs. **b** The top 30 preferred words for the positive signal intensity of subcutaneous target drugs

retinal rupture (95% CI: 4.39, 2.54–7.57). Notably, no ocular disease-specific PTs were associated with the oral dosage form.

Discussion

Semaglutide is unique among GLP- 1 agonists, being the only medication in this class available in both oral and subcutaneous formats. Owing to its proven efficacy and substantial compliance rates, this approach has been endorsed by various authoritative guidelines as a preventive and therapeutic measure for diabetes [17]. In addition, semaglutide has seen increasing use in the domain of weight management, prescribed not only for patients clinically requiring weight loss treatment but also used by individuals outside these medical parameters, which has contributed to a rise in its prescription rates [18, 19]. However, existing research on the safety of semaglutide primarily concentrates on individual dosage forms or fails to differentiate between administration routes. For instance, the SUSTAIN 7 and PIONEER 10 trials, which assessed the subcutaneous and oral formulations respectively, did not conduct a systematic analysis of ocular ADEs [18, 20]. To gather the most comprehensive safety data possible and address this gap in research, we undertook a retrospective pharmacovigilance study that, for the first time,

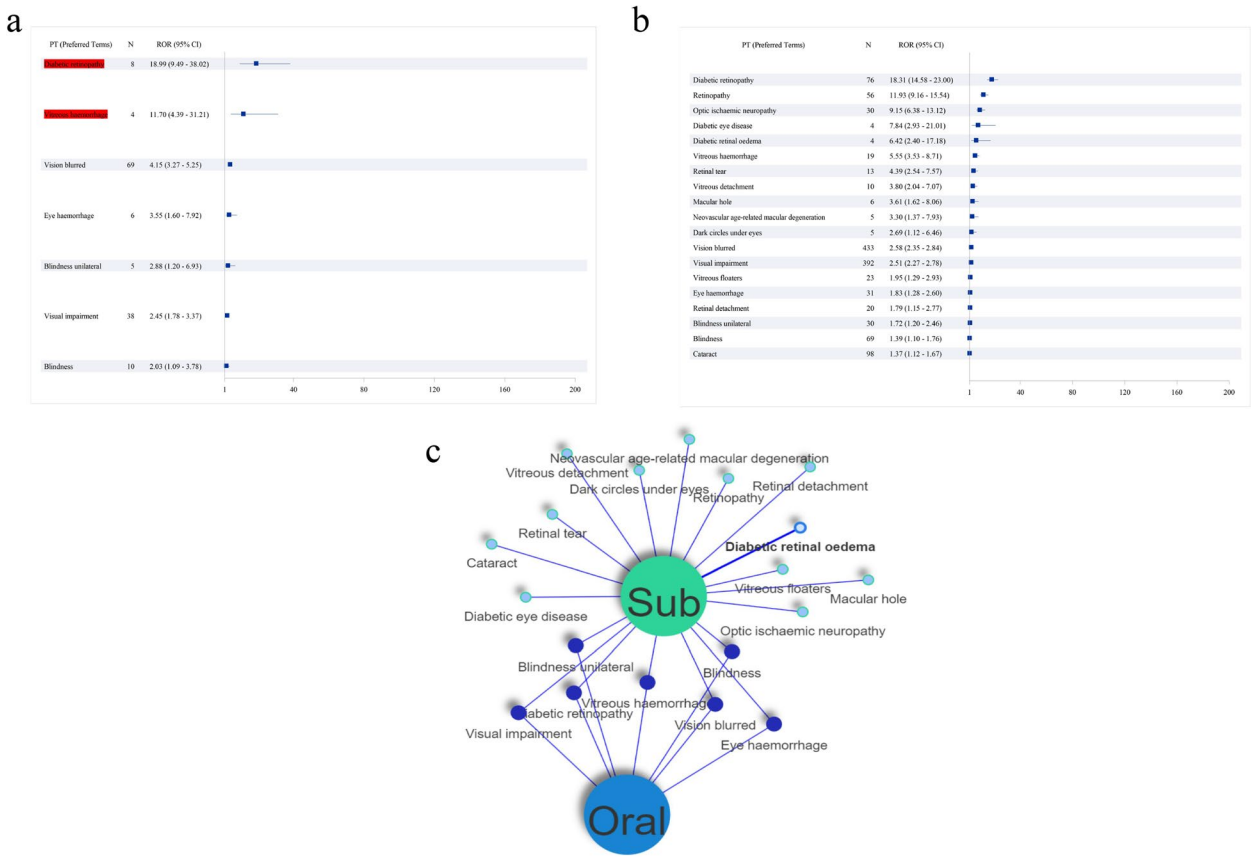

Fig. 5 Unique adverse reaction signals under different routes of administration were analyzed. **a** The top 30 preferred words for the positive signal intensity of oral target drugs. **b** The top 30 preferred words for the positive signal intensity of subcutaneous target drugs. **c** Network diagram of the preferred language for positive signals in different dosage forms

identified formulation-specific risks through pharmacovigilance data. This study was conducted in direct response to the call by Davies et al. to investigate safety variances across different GLP- 1 receptor agonist formulations [21].

With respect to ocular-related ADEs, the study observed an annual increase in reports associated with the subcutaneous form of semaglutide, whereas reports linked to the oral form remained relatively stable. Importantly, the majority of these reports were submitted by purchasers rather than healthcare professionals, which may raise concerns about the data's accuracy and completeness. This pattern could indicate a greater propensity among patients to report adverse reactions directly following the use of semaglutide, or it may point to deficiencies in the reporting practices of healthcare providers. Given that a substantial portion of the reports originated from the United States, further investigation is warranted to understand these reporting trends and the maturity of reporting systems within various regional or cultural contexts.

While the pharmacokinetic properties and therapeutic effects of a drug generally remain consistent across different routes of administration, distinct formulations of the same drug can demonstrate variations in absorption characteristics. In this context, a notable difference in the median onset time of adverse drug events (ADEs) was observed between two patient groups: those on the oral formulation of semaglutide and those on the injectable form. Specifically, the onset time for ADEs associated with the oral formulation is approximately half that observed with the injectable form. Consequently, proactive preventive measures are advisable when prescribing the oral formulation of semaglutide. Furthermore, the recent STEP-HFpEF study highlighted disparities in baseline health status and physical capabilities between genders, with women generally presenting poorer health metrics compared to men. Despite these baseline differences, semaglutide administration at identical dosages has demonstrated a more pronounced effect on weight loss in women [22]. This finding underscores the importance of considering gender-specific responses in the

clinical management of conditions treatable with semaglutides. Our research findings indicate that the proportion of ADEs related to semaglutide use in women (62.72%) is higher than in men (33.67%), suggesting the need for special attention to gender differences in clinical applications. In the ADE reports collected, cases in the 45–64 age group were the most common.

Although confounders were addressed through stratified analysis and the use of ROR methods, the inherent bias of FAERS data, due to its spontaneous reporting nature, cannot be overlooked [23]. Of note, the retinopathy signal intensity (ROR= 1.89) in the 45–64 years group was consistent with the trend of sex differences in the Danish cohort study and the SUSTAIN- 6 trial [24, 25]. Biologically, the reduced clearance of semaglutide in women combined with decreased estrogen levels during menopause may synergistically elevate the risk of retinal microvascular damage [26, 27]. Future studies should incorporate the status of hormone replacement therapy and molecular markers (e.g., VEGF, ER-α expression) to further investigate this hypothesis [28]. However, the lack of precise age-specific details in a large amount of information limits our in-depth understanding of the incidence of ADEs in different age groups. Future studies should utilize accurate age-related data to further explore the different responses to the medication across age groups. In summary, as time progresses and systems improve, the number of ADE reports for semaglutide may increase, and its safety signal spectrum may continually evolve.

Compared to the oral formulation, the subcutaneous injection of semaglutide appeared to report more ADEs, possibly because the subcutaneous formulation was marketed earlier. At the level of PTs, both formulations showed relatively high reports of blurred vision, but the oral formulation did not exhibit a stronger signal than the subcutaneous formulation. In addition to blurred vision, there were also high frequencies of signals for diabetic retinopathy and visual impairment, including more severe adverse event reports such as blindness and unilateral blindness. In these reports, oral semaglutide showed a higher signal strength for diabetic retinopathy (= 8, 95% CI: 18.99, 9.49–38.02) and vitreous hemorrhage (= 4, 95% CI: 11.70, 4.39–31.21), though the frequencies were not high; whereas the frequency of blurred vision (= 69, 95% CI: 4.15, 3.27–5.25) was higher, with a moderate signal strength. However, there was a certain correlation between oral semaglutide and blindness (= 10, 95% CI: 2.03, 1.09–3.78).

After comparative analysis, we found that subcutaneous injections report retinal-related adverse events (ADEs) more frequently than oral medications. These include diabetic retinopathy (= 76, 95% CI: 18.31, 14.58–23.00), retinopathy (= 56, 95% CI: 11.93, 9.16–15.54), and retinal detachment (= 20, 95% CI: 1.79, 1.15–2.77). The differences between subcutaneous and oral forms of semaglutide in retinal ADEs might stem from variations in pharmacokinetics. Kapitza et al. reported that subcutaneous semaglutide reaches its peak concentration within 1 to 3 days, whereas oral tablets peak between 30 to 60 minutes and exhibit lower bioavailability [29]. These distinctions could intensify fluctuations in blood glucose levels, potentially triggering known stressors that affect retinal vasculature. Consequently, this could lead to a further progression of certain retinal diseases in patients using GLP- 1RAs [30]. This finding aligns with Vilsbøll et al.'s hypothesis that blood glucose variability in subcutaneous forms may accelerate retinopathy [15]. Additionally, it is crucial to understand that the ROR indicates the relative risk of adverse reactions associated with semaglutide use; however, it should not be directly interpreted as the actual probability of these adverse reactions occurring. This distinction emphasizes the need for comprehensive risk assessment and patient-specific considerations in clinical practice.

The limitations of this study can be attributed to several factors: First, as the FAERS database is a spontaneous reporting system, the quality and quantity of the information it contains are not strictly controlled. Common limitations in pharmacovigilance studies, such as incomplete patient information in reports, duplicate reports due to different reporters, difficulty in identifying risk levels, and challenges in quantifying risks, are also unavoidable in this study. Secondly, the study did not consider certain potential confounding factors, such as drug interactions, previous health conditions of the patients, and the use of multiple medications. Lastly, although the use of analytical methods has aided in our deeper understanding of the relationship between drugs and ADEs, it must be emphasized that well-designed clinical trials remain crucial in establishing causal relationships, and further research needs to be conducted through extensive clinical studies. Despite the limitations of data mining from the FAERS in pharmacovigilance research, this study provides a comprehensive comparative analysis of eye-related ADEs under different formulations of semaglutide, offering a rich evidence base for future clinical research and safe real-world use.

Conclusion

The pharmacovigilance system has identified both common and uncommon ocular side effects associated with different formulations of semaglutide, highlighting variations across gender, age groups, and time of onset. It is advisable that patients be closely monitored for symptoms such as blurred vision and visual impairment

during the first month of treatment, especially concerning retinopathy linked to subcutaneous injections. The existing evidence affirms the safety and tolerability of various semaglutide formulations, with the majority of ADEs being non-severe. Consequently, we advocate for a prudent expansion of new indications and meticulous clinical management to extend substantial benefits to a wider patient demographic.

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Authors' contributions
Yongmei Huang, Guosong Wu and Tao Zhao conceived the study idea and performed data cleaning and literature review; Guosong Wu, Tao Zhao, Liting Zheng and Yiyun Feng contributed to the drafting and critical revision of the knowledge content work. Guosong Wu, Tao Zhao and Min Lao conducted the analysis, created graphics and tables, provided critical reviews and revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This article is based on open-label data and does not contain any new studies conducted by authors on human participants or animals and does not require ethical approval.
All the study participants provided their informed consent since there is no personal data, publication consent is not requested.

Competing interests
The authors declare no competing interests.

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