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Assessing the shadows

A meta-analysis of GLP-1 agonists and suicidal ideation

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Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 agonist) have revolutionized the treatment of obesity. However, regulatory agencies have reported an association with suicidality. To the best of our knowledge, this is the first meta-analysis to assess the association between GLP-1 agonist use, suicidal ideation, and suicide completion. We aimed to assess the same in patients with diabetes and obesity.

Methods: We searched 6 databases for relevant articles, from the first published article to October 2024. The keywords used were GLP-1 agonists, suicidal ideation, suicide, suicidal behavior, semaglutide, liraglutide, tripeptide, exenatide, and lixisenatide. We identified 354 studies and 126 stands after the removal of duplicates, of which 23 were eligible, and only 12 studies were included in the final meta-analysis.

Results: No significant statistical difference was found in suicidal ideations in patients on GLP-1 agonists compared to their counterparts on other obesity and diabetes drugs (odds ratio [OR], 1.0; 95% confidence interval [CI]: 1.0–1.0). No significant difference was observed between patients on GLP-1 agonists and their counterparts regarding complete suicide (OR, 1.77; 95% CI: 0.80–3.91). In a subgroup analysis, suicide was higher among patients on liraglutide compared to their counterparts on semaglutide (OR, 1.48; 95% CI: 1.17–1.89). No significant statistical difference was observed when comparing monjaro and semaglutide (OR, 0.98; 95% CI: 0.94–1.03).

Conclusion: No significant statistical difference was found between GLP-1 agonists and other obesity and diabetes drugs regarding suicide/suicidal ideation. In a subgroup analysis, suicide was higher in patients on liraglutide compared to semaglutide, with no significant difference between semaglutide and monjaro. Randomized controlled trials that assess the association between GLP-1 agonists and suicidality are highly recommended.

Abbreviations: CI = confidence interval, GLP-1 = glucagon-like peptide-1, OR = odds ratio, RCT = randomized controlled trial.

Keywords: glucagon-like receptors-1 agonists, liraglutide, semaglutide, suicidal ideation, suicide, tirzepatide

1. Introduction

Glucagon-like peptide-1 (GLP-1) agonists have significantly changed the management of diabetes and obesity, leading to a paradigm shift (also called the breakthrough of 2023). Exenatide was the first approved GLP-1 agonist (2005), but more medications with a longer duration of action and more potency have appeared in the market, while others are on the horizon.[1,2]

There has been a rapid evolution in the field of GLP-1 agonists because liraglutide (the most commonly prescribed GLP-1 agonist for obesity) is now replaced with once-weekly semaglutide and twincretin tirzepatide, which is a GLP-1 agonist and glucose-dependent insulinotropic polypeptide combination.[3]

Obesity and diabetes mellitus are among the 10 top economically burdensome diseases, and their prevalence is

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This study did not require ethical approval according to the guidelines of the Local Research Ethics Committee in University of Tabuk.

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expanding worldwide. Therefore, the market for GLP-1 agonists has expanded significantly.[4] However, despite the potential benefits and cardiac and renal protection, many adverse events are of concern, ranging from tolerable gastrointestinal side effects to raised living enzymes with lotiglipron and thyroid malignancy risk.[5,6] However, the most significant issue that could jeopardize the patient's safety and health is the report to the European Medicines Agency regarding the possible association between GLP-1 agonists and suicidal behavior.[7]

GLP-1 agonists can improve self-esteem and body image, and positively influence the mental status of many individuals. On the other hand, rapid weight loss can increase suicidal thoughts and ideation, and possible mechanisms could involve high cortisol and norepinephrine levels. The identity changes and unmet expectations following weight loss are other contributors.[8,9]

Suicidal thoughts are ideas raised in one consciousness willingly or not; they are very common, and more than 1 in 5 people experience them at some point in their life. A suicide attempt is an attempt to end life, while suicide is death resulting from suicide attempts. Importantly, suicide and suicidal ideation are weakly correlated and people with suicidal thoughts live their entire lives without suicidal attempts.[10,11]

Despite the above-mentioned benefits of GLP-1 agonists and their effectiveness in weight reduction and glycemic control, there is increasing concern regarding their association with suicidal ideation. To the best of our knowledge, this is the first meta-analysis to assess the relationship between suicidality and GLP-1 agonist use. This meta-analysis aimed to investigate the association between GLP-1 agonists used in diabetes and weight management, suicidal thoughts, and suicide.

2. Subjects and methods

2.1. Eligibility criteria according to Population, Intervention, Comparison, Outcomes, and Study design (PICOS)

This study aimed to assess the association between *Population*: adults patients on GLP-1 agonists; *Intervention*: glucagon-like receptor 1 agonists; *Comparison*: adults on other drugs or placebo; *Outcomes*: suicidal ideation, and suicide; *Study design*: meta-analysis.

2.2. Inclusion criteria

Studies were eligible if they were randomized controlled trials (RCTs), prospective and retrospective studies, case-control, and cross-sectional studies, and compared suicide/suicide ideation among patients on GLP-1 agonists and other therapy or placebo. No limitations were applied to the date of publication (from the first publication up to October 2024). Studies must compare suicide/suicidal ideation among patients taking GLP-1 antagonists and other drugs or placebo.

2.3. Exclusion criteria

Case reports, case series, expert opinions, protocols without results, reviews, and editorials were excluded from the analysis.

2.4. Literature search

The detailed database search strategies are provided in Table S1, Supplemental Digital Content, https://links.lww.com/MD/Q735.

2.5. Literature search and data extraction

The 2 authors searched PubMed, MEDLINE, Web of Science, EBSCO, Google Scholar, and Cochrane Library from the date of the first inception up to October 2024. The keywords GLP-1 agonists semaglutide, liraglutide, tirzepatide, exenatide, and lixisenatide were used. Additionally, we screened the titles, abstracts, and references of the included studies for relevant articles. We identified 354 studies and 126 stands after the removal of duplicates, of which 23 were eligible, and only 12 studies were included in the final meta-analysis (Fig. 1).

2.6. Data extraction

The author's name, year, and country of publication, number of participants in the GLP-1 agonist arm and control groups, and number of suicides and suicidal ideation were recorded in an Excel sheet (Tables 1 and 2).

2.7. Risk of bias assessment

The Newcastle Ottawa Scale risk of bias assessed the risk of bias in the included studies.[24] All the included studies were of medium/good quality (Table 3).

2.8. Statistical analysis

The data were analyzed using the most recent version of the Review Manager (RevMan) version 5.4; The Cochrane Collaboration, Copenhagen, Denmark. We pooled 16 cohorts from the 12 retrospective studies. The dichotomous data were entered manually, and the random effect was due to substantial heterogeneity (95% in completed suicide, and 99% in suicidal ideation, while the heterogeneity was 90% when comparing onjaro and semaglutide). The fixed effect was applied in the semaglutide and liraglutide comparisons due to the 0% heterogeneity; The chi-square test, weighted average effect size (Z), and standard difference were applied, and a sub-analysis was conducted to address heterogeneity. Statistical significance was set at $P < .05$.

3. Results

3.1. Characteristics of the included studies

Chen et al[12] assessed different age groups with a female predominance not matched for age; the duration was 18 years. Hurtado et al[13] assessed the suicide rate among patients treated with GLP-1 agonists and sodium-glucose co-transporter inhibitors for 6 years, GLP-1 agonist users were young females, obese, and had more anxiety, depression, and sleep disorders. Kerem and Stokar[14] assessed adolescents matched for age and sex using GLP-1 agonists or a lifestyle followed for 5 years. O'Neil et al[15] conducted a post hoc analysis of phase 2 and phase 3 double-blinded RCTs with a low risk of bias and included 5325 participants who received either liraglutide 3 mg or placebo. Wang et al[16] investigated suicide among patients taking semaglutide and other diabetes medications using propensity matching and followed up for 18 months. Nassar et al[17] used a large database based on real-world data including patients with type 2 diabetes, the study compared GLP-1 agonists with dipeptidyl peptidase-4 inhibitors, patients on GLP-1 are more likely young females, while Ueda et al[18] used a registry data with 2.5 ± 1.7 years follow-up comparing GLP-1 agonists and SGLT-2 inhibitors. In the present study Anson et al[19] compared tirzepatide and semaglutide use among patients with/without type 2 diabetes matched for age and gender, and followed for 1 year. Guirguis et al[20] compared different GLP-1 agonists with different age groups and males:females ratios and followed form from pharmacovigilance measures and unmasking

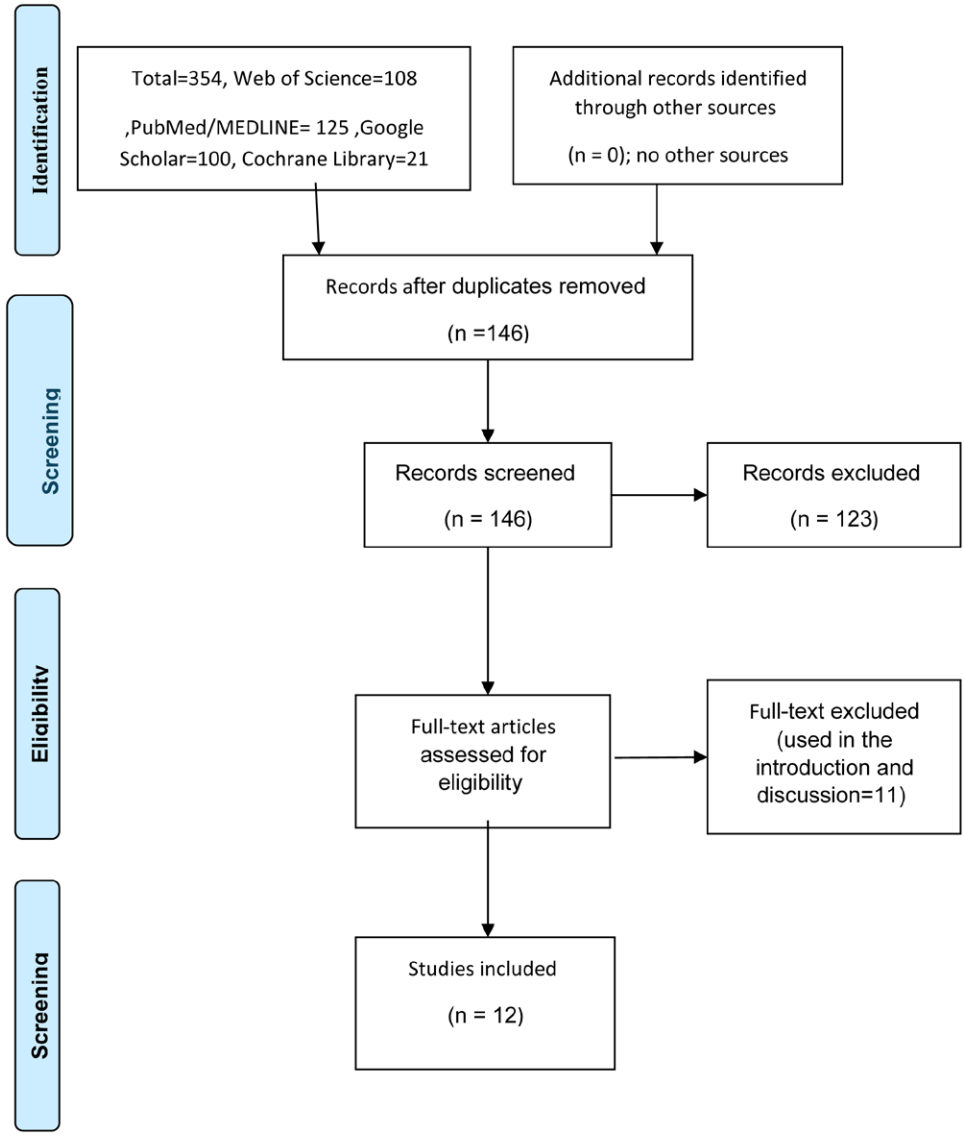

Figure 1. A comparison of suicide and suicidal ideation among patients on GLP-1 agonists and other obesity/diabetes drugs (the PRISMA chart). PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table 1

Suicidal ideation among patients on GLP-1 agonists.

References	Country	Type of study	On GLP-1 agonists	Control subjects	Events, GLP-1 agonists	Events, controls
Suicidal ideation among patients on GLP-1 agonists and other obesity and diabetes drugs						
Chen et al[12]	China	Retrospective	543	287,604	275	94,409
Hurtado et al[13]	Spain	Retrospective	2316	9053	10	17
Kerem and Stokar[14]		Retrospective	3456	3456	77	89
O'Neil et al[15]	USA	RCT, liraglutide	3270	1832	34	19
Wang et al[16]	USA	Retrospective	52,783	52,783	60	266
Suicide among patients on GLP-1 agonists and other obesity and diabetes drugs						
Chen et al[12]	China	Retrospective	543	287,604	50	77,900
Kerem and Stokar[14]		Retrospective	3456	3456	10	11
Nassar et al[17]	USA, attempts	Retrospective	373,041	372,944	106	230
Ueda et al[18]	Sweden	Retrospective	124,517	174,036	77	71

GLP-1 = glucagon-like peptide-1, RCT = randomized controlled trial.

analysis 2005 to 2023. Ruggiero et al[21] used the European Pharmacovigilance Database followed for 5.5 years; the comparison was between semaglutide and liraglutide (more females) unmatched for age groups. Similarly, Schoretsanitis et al[22] assessed suicide and suicidal ideation among patients from the World Health Organization from inception to September 2023; the reports compared semaglutide and liraglutide matched for age. However, there were more females in the liraglutide group,

while Tobaiqy and Elkout[23] used pharmacovigilance analysis of individual case safety reports from Europe and compared liraglutide, semaglutide, and tripeptide from January 2021 to May 2023; the patients were not matched for age and sex.

3.2. GLP-1 agonists and suicidal ideation

Regarding GLP-1 agonists and suicidal ideation, we included 5 studies[12–16] (510,962 patients included with 1399 suicidal ideations observed). Suicidal ideations were similar among patients on GLP-1 agonists and their counterparts on other obesity and diabetes drugs (odds ratio [OR], 1.0; 95% confidence interval [CI]: 1.0–1.0, chi-square, 64.42, and *P*-value for overall effect, .40). Significant heterogeneity was observed (I^2 = 94%, *P*-value for heterogeneity <.001, and standard difference = 4) (Fig. 2).

3.3. GLP-1 agonists and suicide

In the present meta-analysis, 4 studies assessed completed suicide,[12,14,17,18] with no significant difference between patients on GLP-1 agonists and their counterparts regarding complete suicide (OR, 1.77; 95% CI: 0.80–3.91, chi-square, 65.09, and *P*-value for overall effect, .16). Substantial heterogeneity was observed (I^2 = 95%, *P*-value for heterogeneity <.001, and standard difference = 4) (Fig. 3). In a sub-analysis to address heterogeneity, Hurtado et al reported the highest heterogeneity.

3.4. Suicide among patients on semaglutide and liraglutide

We included 4 studies[20–23] (3542 patients included with 321 suicidal events observed). Suicide was higher among patients on liraglutide compared to their counterparts on semaglutide (OR, 1.48; 95% CI: 1.17–1.89, chi-square, 2.53, and *P*-value for overall effect, .001). No heterogeneity was found (I^2 = 0%, *P*-value for heterogeneity = .47, standard difference = 3) (Fig. 4).

3.5. Suicide among patients on semaglutide and tripeptide

In a sub-analysis including patients on monjaro and semaglutide,[19,20,23] no significant statistical difference was observed in suicide (OR, 0.98; 95% CI: 0.94–1.03, chi-square, 19.35, and *P*-value for overall effect, .048). Significant heterogeneity was observed (I^2 = 90%, *P*-value for heterogeneity <.001,

Table 2

Suicide among patients on semaglutide, liraglutide, and tirzepatide (monjaro).

References	Country	Type of study	Semaglutide (total)	Liraglutide (total)	Monjaro (total)	Semaglutide (events)	Liraglutide (events)	Monjaro (events)
Anson et al[19]	UK	Retrospective	13/4223	Not assessed	4223	13	Not assessed	7
Guirguis et al[20]	UK	Adverse events reporting system	1221	1519	269	76	143	6
Ruggiero et al[21]	Italy, attempts	Retrospective	86	90	Not assessed	67	60	Not assessed
Ruggiero et al[21]	Italy, suicide	Retrospective	86	90	Not assessed	3	5	Not assessed
Schoretsanitis et al[22]	USA, ideation	Retrospective	107	162	Not assessed	94	116	Not assessed
Schoretsanitis et al[22]	USA, suicide	Retrospective	107	162	Not assessed	6	19	Not assessed
Tobaiqy and Elkout[23]	Saudi Arabia	Retrospective	210	147	15	40	29	4

Table 3

Newcastle Ottawa Scale risk of bias of the included studies.

References	Selection	Compatibility	Exposure	Total score
Chen et al[12]	4	2	2	8
Hurtado et al[13]	3	2	2	7
Kerem and Stokar[14]	4	2	2	8
Wang et al[16]	3	2	3	8
Nassar et al[17]	4	2	2	8
Ueda et al[18]	3	2	2	7
Anson et al [19]	4	2	3	9
Guirguis et al[20]	4	2	3	9
Ruggiero et al[21]	4	2	2	8
Schoretsanitis et al[22]	4	2	2	8
Tobaiqy and Elkout[23]	4	1	2	7

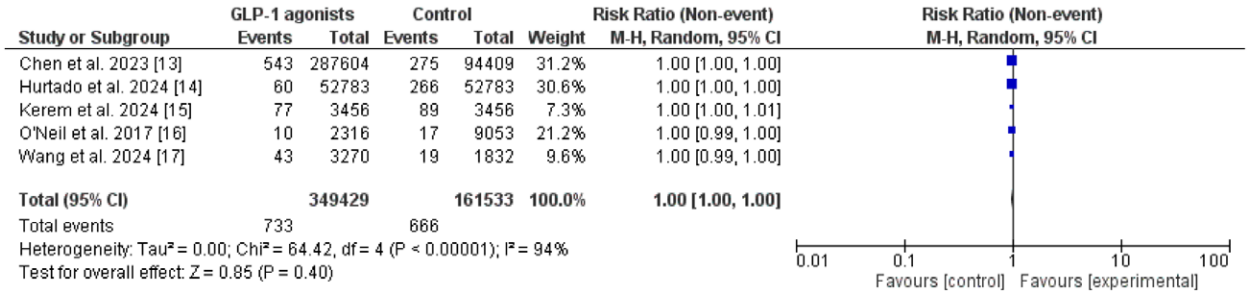

Figure 2. Suicidal ideation among patients on GLP-1 agonists and control subjects. CI = confidence interval, GLP-1 = glucagon-like peptide-1.

and standard difference = 2). The highest heterogeneity was observed in the study by Guirguis et al (Fig. 5).

4. Discussion

GLP-1 receptor agonists were first approved for diabetes medications and were recently approved for weight management. The prescription of GLP-1 agonists is increasing owing to concerns about their association with suicide and suicidal ideation.[25,26] The observed imbalance between GLP-1 agonists, depression, and suicide in phase 2 and phase 3 clinical trials is difficult to assess because suicide is rarely assessed in a preclinical setting, and patients with suicide risk were excluded from these randomized control trials.[27] Data on the association between GLP-1 agonists and suicidal ideation are scarce, and a recent systematic review found a reduction in suicidal ideation among GLP-1 agonist users through inflammation reduction and antioxidant effects.[28] Neurogenesis, neuroinflammation, synaptic function, and neurotransmitter modulation may explain the association between depression/suicide and GLP-1 agonists.[29] We found no differences between patients taking GLP-1 agonists and their counterparts taking other medications regarding suicidal ideation (OR, 1.0; 95% CI: 1.0–1.0), and suicide (OR, 1.77; 95% CI: 0.80–3.91). Similarly, no significant statistical difference was found between monjaro and semaglutide (OR, 0.98; 95% CI: 0.94–1.03). However, suicide was lower among patients taking semaglutide than among those taking liraglutide (OR, 1.48; 95% CI: 1.17–1.89). Our findings confirmed the observations of regulatory agencies from the United States and Europe, in which no causal association exists between GLP-1 agonists and suicidality.[30–32]

In this meta-analysis, concerns regarding the association between GLP-1 agonists and suicide were not shown, and GLP-1 agonists have a positive influence on obesity comorbidities, including diabetes control, beneficial effects on dyslipidemia, and high blood pressure.[33] Furthermore, GLP-1 agonists are not associated with oily stool, diarrhea, fecal urgency, or congenital anomalies observed with other obesity medications.[34] The first GLP-1 agonist to be approved for obesity management was liraglutide in 2014, followed by semaglutide in 2021 and tirzepatide in 2022.[35] In the present meta-analysis, no significant difference was observed between the semaglutide and tripeptide groups. However, greater suicidality was observed in the liraglutide arm than in the semaglutide arm. The current findings are in line with previous recommendations for monitoring SAXENDA for suicidal behavior and depression.[15,36] Our study supports previous reports on semaglutide[37] and tirzepatide.[38]

Previous studies showed that semaglutide was more cost-effective than liraglutide for treatment per 1% of body weight reduction.[39] Importantly, evidence from a RCT showed that semaglutide was more effective than semaglutide for weight control among patients with diabetes mellitus with tirzepatide.[40]

The strength of this meta-analysis is that it is the first to assess the association between GLP-1 agonists and suicidality

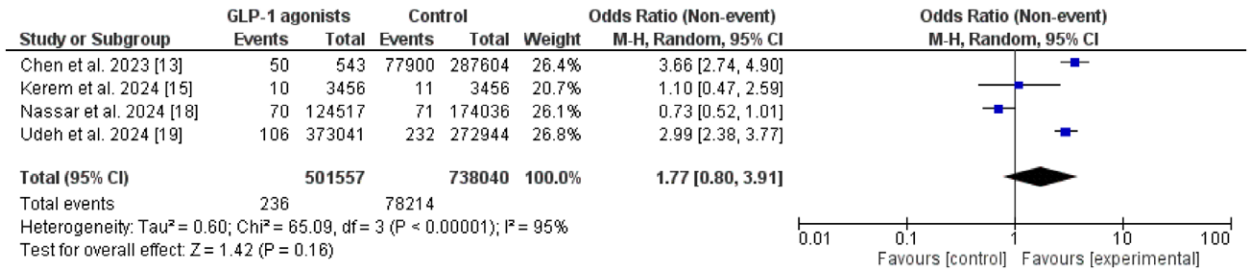

Figure 3. Suicide among patients on GLP-1 agonists and control subjects. CI = confidence interval, GLP-1 = glucagon-like peptide-1.

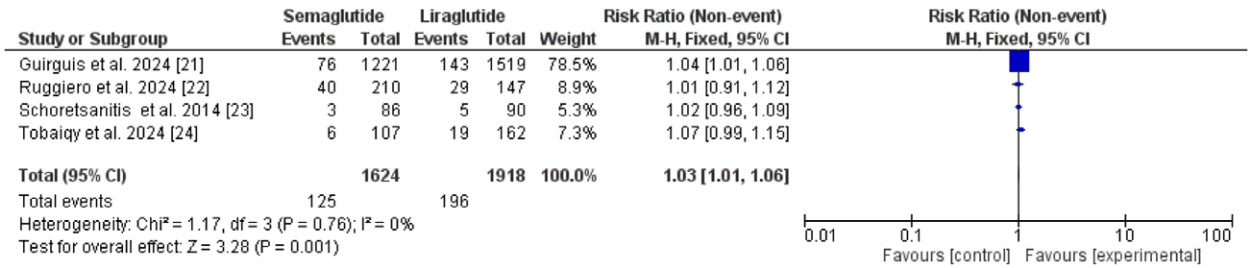

Figure 4. Suicide among patients on semaglutide and liraglutide. CI = confidence interval.

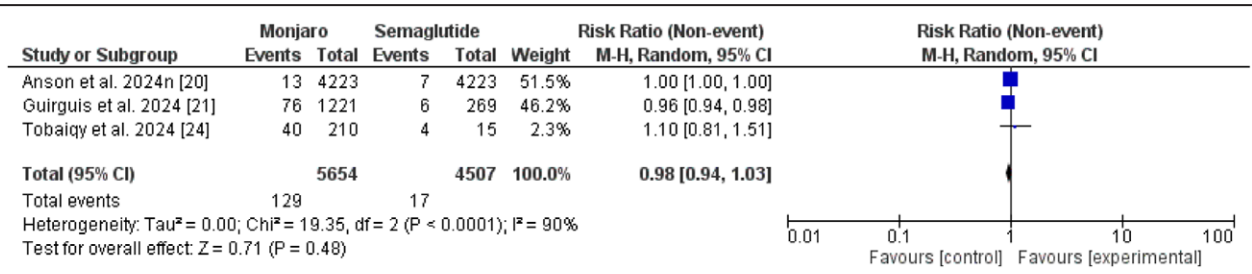

Figure 5. Suicidal ideation among patients on monjaro and semaglutide. CI = confidence interval.

and includes the most recent evidence to inform the scientific community about this important healthcare problem.

4.1. Study limitations

The current meta-analysis was limited by the high heterogeneity observed, observational nature of the included studies, and small number of studies included.

4.2. Conclusion

No significant statistical difference was found in suicide, suicidal ideation in patients taking GLP-1 agonist, and other obesity and diabetes medications. In a subgroup analysis, suicide was higher in patients on liraglutide compared to semaglutide with no significant difference between semaglutide and monjaro. A RCT that assess the association between GLP-1 agonists and suicidality is highly recommended.

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