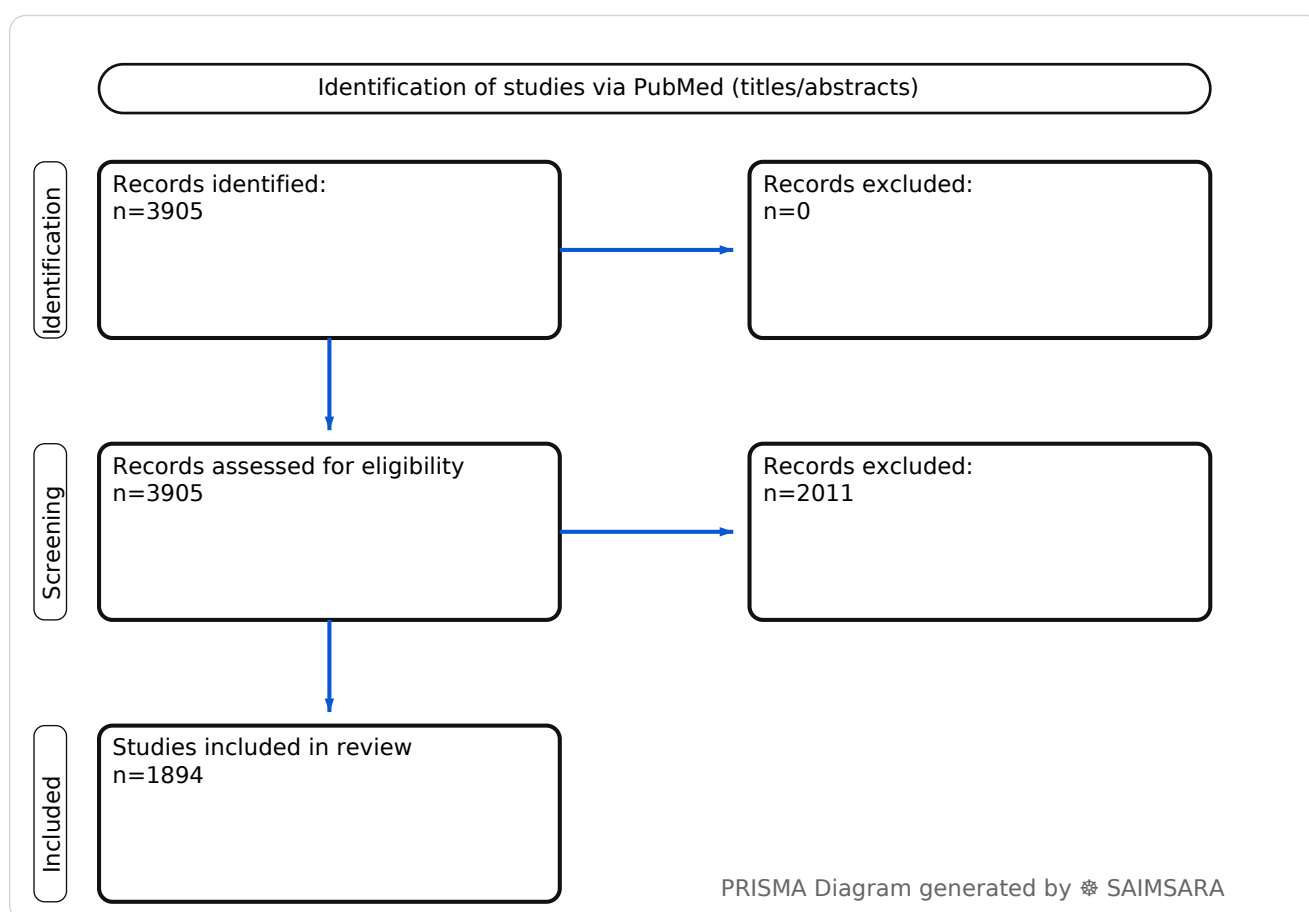


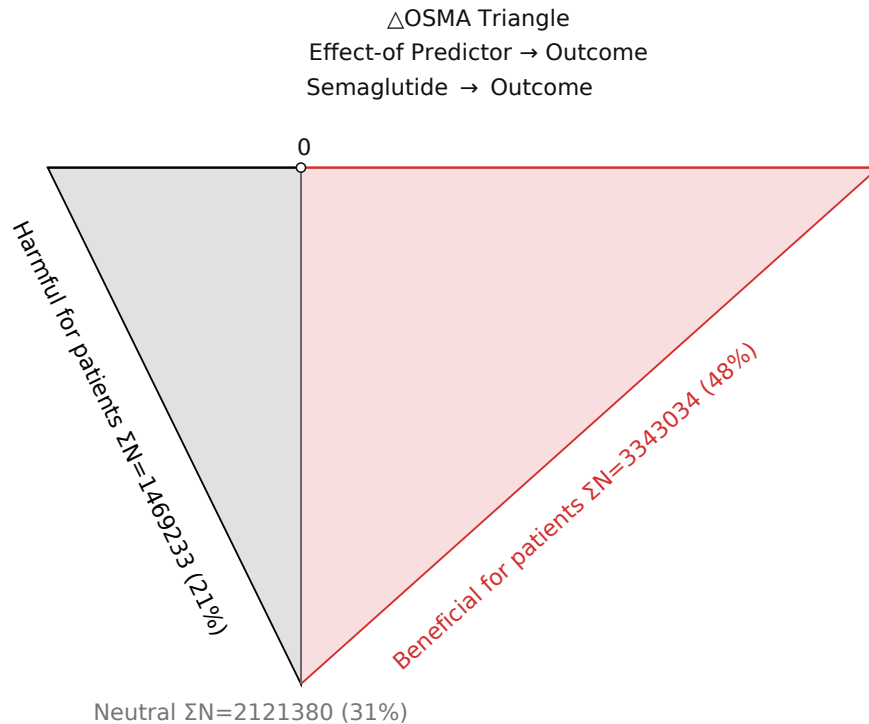
Semaglutide: Systematic Review with SAIMSARA.

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Review Stats

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- Keyword Gate: Fuzzy ($\geq 60\%$ of required terms, minimum 2 terms matched in title/abstract)
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△OSMA Triangle generated by SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): (LLM-only)

Frame: Effect-of Predictor → Outcome • *Source:* PubMed

Outcome: Outcome Typical timepoints: 12-mo, 6-mo. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, qol.

Predictor: Semaglutide — exposure/predictor. Doses/units seen: 0.5 mg, 2.4 mg, 3 mg, 10 mg, 1.0 mg, 7.2 mg.... Routes seen: oral, subcutaneous, sc, iv.... Typical comparator: control, the glp-1 ras group two years, the sleeve gastrectomy group, other weight loss....

- **1) Beneficial for patients** — Outcome with Semaglutide — [5], [8], [10], [11], [13], [14], [16], [21], [30], [33], [38], [39], [47], [53], [55], [56], [58], [59], [61], [63], [66], [67], [69], [72], [76], [80], [96], [101], [103], [107], [109], [112], [118], [119], [122], [124], [127], [129], [130], [131], [132], [135], [141], [144], [150], [152], [155], [156], [157], [160], [161], [162], [164], [165], [166], [167], [168], [169], [170], [171], [172], [173], [176], [177], [178], [179], [183], [184], [186], [190], [192], [193], [195], [198], [200], [202], [205], [208], [209], [210], [214], [215], [216], [217], [219], [223], [226], [227], [232], [233], [237], [239], [241], [246], [255], [258], [259], [261], [270], [272], [273], [277], [283], [284], [287], [288], [290], [291], [298], [300], [304], [306], [307], [308], [309], [310], [312], [317], [318], [319], [320], [321], [322], [323], [324], [325],

[326], [327], [328], [329], [332], [333], [334], [337], [340], [342], [343], [345], [348], [354], [356], [363], [366], [367], [369], [370], [373], [375], [379], [382], [384], [386], [390], [397], [398], [401], [409], [413], [416], [427], [434], [435], [436], [437], [438], [442], [448], [452], [453], [457], [458], [461], [463], [464], [466], [469], [473], [474], [481], [493], [495], [497], [499], [503], [513], [516], [520], [521], [522], [524], [526], [530], [534], [535], [537], [541], [542], [544], [546], [547], [549], [550], [551], [556], [559], [561], [562], [563], [564], [565], [567], [571], [572], [573], [574], [582], [583], [584], [586], [589], [592], [594], [596], [602], [603], [604], [605], [613], [618], [620], [624], [625], [626], [627], [643], [649], [658], [673], [678], [682], [683], [687], [692], [694], [695], [697], [699], [700], [703], [709], [713], [719], [722], [723], [725], [734], [735], [736], [737], [745], [748], [750], [753], [757], [759], [760], [761], [762], [763], [764], [771], [772], [784], [786], [787], [796], [800], [801], [804], [805], [808], [810], [813], [814], [816], [817], [818], [819], [821], [822], [823], [834], [845], [847], [851], [853], [854], [855], [857], [859], [860], [864], [865], [868], [871], [872], [874], [881], [882], [883], [886], [887], [888], [890], [891], [892], [894], [895], [896], [898], [899], [900], [901], [902], [903], [906], [907], [909], [910], [911], [912], [913], [914], [918], [919], [920], [923], [924], [926], [927], [929], [930], [931], [932], [933], [934], [936], [938], [942], [943], [944], [945], [947], [948], [949], [950], [951], [952], [953], [955], [957], [959], [961], [963], [964], [966], [968], [969], [970], [972], [983], [984], [990], [991], [995], [1000], [1001], [1002], [1009], [1012], [1016], [1023], [1025], [1033], [1034], [1038], [1040], [1041], [1044], [1047], [1049], [1050], [1051], [1062], [1070], [1072], [1074], [1076], [1077], [1080], [1085], [1092], [1094], [1098], [1102], [1104], [1105], [1108], [1109], [1111], [1114], [1116], [1117], [1118], [1121], [1126], [1127], [1128], [1131], [1132], [1133], [1140], [1142], [1147], [1148], [1152], [1167], [1168], [1169], [1176], [1177], [1178], [1182], [1184], [1185], [1186], [1188], [1191], [1194], [1195], [1200], [1202], [1203], [1208], [1211], [1212], [1213], [1214], [1215], [1216], [1217], [1218], [1220], [1221], [1222], [1224], [1225], [1226], [1228], [1232], [1233], [1234], [1237], [1238], [1242], [1243], [1245], [1248], [1256], [1258], [1262], [1263], [1274], [1277], [1287], [1288], [1289], [1290], [1292], [1293], [1294], [1296], [1301], [1305], [1308], [1311], [1315], [1319], [1323], [1325], [1327], [1328], [1330], [1332], [1334], [1336], [1337], [1339], [1340], [1346], [1348], [1349], [1350], [1351], [1371], [1379], [1381], [1385], [1388], [1389], [1391], [1398], [1401], [1403], [1405], [1406], [1407], [1408], [1410], [1413], [1414], [1415], [1417], [1418], [1419], [1420], [1422], [1425], [1429], [1430], [1431], [1433], [1434], [1439], [1441], [1444], [1448], [1449], [1451], [1452], [1453], [1454], [1455], [1456], [1458], [1459], [1460], [1461], [1462], [1463], [1464], [1465], [1466], [1467], [1469], [1470], [1471], [1472], [1473], [1474], [1475], [1478], [1479], [1480], [1481], [1483], [1484], [1486], [1492], [1493], [1495], [1497], [1500], [1502], [1503], [1504], [1509], [1512], [1513], [1514], [1515], [1517],

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ΣN=3343034

- **2) Harmful for patients** — Outcome with Semaglutide — [4], [9], [12], [22], [23], [52], [78], [92], [99], [114], [133], [139], [151], [175], [187], [188], [196], [207], [262], [265], [274], [286], [295], [302], [303], [313], [330], [347], [353], [361], [362], [372], [412], [414], [433], [459], [467], [475], [476], [477], [483], [487], [505], [511], [514], [518], [527], [531], [532], [538], [539], [552], [557], [575], [590], [597], [606], [628], [650], [690], [691], [701], [726], [732], [733], [746], [781], [795], [797], [807], [820], [826], [827], [836], [844], [849], [869], [877], [878], [884], [904], [937], [939], [954], [962], [1013], [1020], [1057], [1059], [1096], [1130], [1153], [1180], [1306], [1309], [1310], [1324], [1335], [1394], [1435], [1437], [1445], [1511], [1539], [1883] —
ΣN=1469233

- **3) No clear effect** — Outcome with Semaglutide — [1], [2], [3], [6], [7], [15], [17], [18], [19], [20], [24], [25], [26], [27], [28], [29], [31], [32], [34], [35], [36], [37], [40], [41], [42], [43], [44], [45], [46], [48], [49], [50], [51], [54], [57], [60], [62], [64], [65], [68], [70], [71], [73], [74], [75], [77], [79], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [93], [94], [95], [97], [98], [100], [102], [104], [105], [106], [108], [110], [111], [113], [115], [116], [117], [120], [121], [123], [125], [126], [128], [134], [136], [137], [138], [140], [142], [143], [145], [146], [147], [148], [149], [153], [154], [158], [159], [163], [174], [180], [181], [182], [185], [189], [191], [194], [197], [199], [201], [203], [204], [206], [211], [212], [213], [218], [220], [221], [222], [224], [225], [228], [229], [230], [231], [234], [235], [236], [238], [240], [242], [243], [244], [245], [247], [248], [249], [250], [251], [252], [253], [254], [256], [257], [260], [263], [264], [266], [267], [268], [269], [271], [275], [276], [278], [279], [280], [281], [282], [285], [289], [292], [293], [294], [296], [297], [299], [301], [305], [311], [314], [315], [316], [331], [335], [336], [338], [339], [341], [344], [346], [349], [350], [351], [352], [355], [357], [358], [359], [360], [364], [365], [368], [371], [374], [376], [377], [378], [380], [381], [383], [385], [387], [388], [389], [391], [392], [393], [394], [395], [396], [399],

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— ΣN=2121380

1) Introduction

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has emerged as a transformative therapeutic agent, primarily recognized for its efficacy in managing type 2 diabetes mellitus (T2DM) and obesity. Its mechanism of action extends beyond glycemic control, influencing various metabolic, cardiovascular, renal, and even neurological pathways. This paper synthesizes recent findings to provide a comprehensive overview of semaglutide's multifaceted effects, its applications across diverse patient populations, and associated safety considerations.

2) Aim

The aim of this systematic review is to synthesize the current evidence regarding the efficacy, safety, and broader therapeutic potential of semaglutide across various clinical and preclinical contexts.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields. Studies designated as "Mixed" or "Not specified" for study type/directionality, as well as smaller sample sizes (e.g., N=1-3 cases), introduce a higher risk of bias and limit generalizability. Retrospective cohort studies are prone to selection and confounding biases, while experimental animal models may not directly translate to human outcomes. Randomized controlled trials (RCTs) and large prospective cohorts generally offer higher levels of evidence.

4) Results

4.1 Study characteristics

The included studies comprise a diverse range of designs, including numerous randomized controlled trials (RCTs) [8, 17, 21, 24, 25, 29, 50, 74, 95, 113, 1170, 1191, 130, 155, 157, 168, 169, 173, 174, 178, 208, 209, 219, 239, 270, 283, 308, 309, 319, 325, 343, 354, 364, 366, 380, 404, 405, 416, 447, 484, 488, 497, 499, 503, 507, 511, 517, 519, 546, 547, 550, 553, 570, 573, 583, 586, 587, 602, 603, 613, 623, 626, 653, 763, 828, 895, 955, 974, 1004, 1052, 1154, 1170, 1191, 125, 1346, 1378, 1714, 1729, 1741, 1751], large cohort studies (some retrospective) [5, 10, 12, 14, 20, 23, 27, 45, 46, 47, 51, 56, 60, 65, 67, 69, 78, 81, 83, 87, 100, 106, 109, 110, 118, 119, 125, 129, 130, 134, 135, 141, 145, 147, 150, 152, 154, 159, 161, 165, 166, 167, 170, 171, 172, 177, 179, 182, 183, 184, 187, 190, 192, 193, 195, 196, 197, 198, 199, 201, 202, 203, 205, 206, 207, 212, 214, 224, 229, 233, 238, 239, 252, 255, 256, 260, 261, 263, 265, 272, 273, 276, 277, 278, 280, 283, 285, 287, 288, 291, 292, 294, 300, 307, 309, 311, 312, 315, 316, 318, 319, 324, 326, 328, 332, 333, 336, 339, 340, 341, 345, 348, 350, 351, 352, 353, 356, 358, 360, 362, 363, 367, 372, 375, 379, 380, 382, 384, 385, 386, 387, 389,

390, 392, 395, 396, 397, 398, 399, 404, 405, 406, 407, 413, 414, 416, 418, 423, 426, 428, 429, 430, 434, 436, 439, 440, 441, 442, 443, 445, 447, 449, 450, 452, 453, 454, 455, 456, 457, 458, 460, 464, 466, 468, 469, 473, 474, 475, 476, 477, 479, 480, 481, 482, 483, 485, 487, 488, 490, 491, 492, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 507, 509, 510, 511, 512, 517, 519, 521, 522, 526, 527, 528, 529, 530, 532, 535, 536, 537, 542, 544, 545, 546, 547, 549, 550, 552, 554, 556, 557, 561, 563, 564, 565, 566, 567, 568, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 583, 584, 586, 587, 588, 589, 590, 591, 592, 594, 595, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 609, 610, 611, 612, 613, 614, 615, 616, 617, 619, 620, 621, 622, 623, 624, 626, 628, 629, 630, 631, 633, 634, 635, 636, 638, 639, 640, 642, 643, 645, 649, 653, 683, 688, 689, 763, 771, 787, 812, 817, 826, 828, 837, 847, 895, 921, 942, 955, 957, 969, 974, 1004, 1020, 1036, 1052, 1054, 1066, 1087, 1127, 1145, 1147, 1154, 1163, 1169, 1170, 1191, 1199, 1222, 1223, 1230, 1263, 1334, 1338, 1346, 1358, 1378, 1390, 1399, 1404, 1412, 1415, 1434, 1443, 1518, 1521, 1523, 1525, 1526, 1530, 1534, 1543, 1549, 1554, 1567, 1696, 1707, 1709, 1713, 1714, 1716, 1719, 1721, 1729, 1730, 1741, 1751], and experimental studies (often animal models) [2, 32, 37, 42, 48, 65, 70, 73, 76, 114, 115, 121, 123, 138, 140, 143, 148, 149, 156, 158, 162, 173, 174, 186, 188, 191, 194, 199, 232, 235, 257, 259, 266, 268, 269, 279, 281, 282, 305, 308, 314, 320, 321, 338, 341, 352, 360, 366, 368, 376, 377, 383, 385, 394, 399, 410, 419, 432, 450, 456, 458, 460, 468, 473, 496, 500, 509, 511, 529, 536, 570, 577, 578, 587, 588, 591, 595, 601, 607, 609, 616, 622, 630, 631, 636, 639, 645, 653, 921, 957, 974, 1145, 1163, 1338, 1346, 1399, 1709, 1730]. Populations include adults and adolescents with obesity, T2DM, type 1 diabetes (T1D), chronic kidney disease (CKD), cardiovascular disease (CVD), metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH), and various other conditions. Follow-up periods range from weeks to several years, with many studies reporting outcomes at 12 months.

4.2 Main numerical result aligned to the query

Semaglutide treatment for obesity or overweight without type 2 diabetes is associated with a median body weight reduction of 15.3% (range: 13.4% to 19.5%) over approximately one year [98, 107, 1147, 567, 318, 319, 333, 283, 455, 484, 209, 272]. This significant weight loss is observed across various real-world and clinical trial settings.

4.3 Topic synthesis

- **Weight Management:** Semaglutide consistently leads to significant body weight loss (median 15.3%, range 13.4-19.5% over ~1 year in obesity without T2D) [98, 107, 1147, 567, 318, 319, 333, 283, 455, 484, 209, 272]. It reduces fat mass while preserving lean muscle mass [166, 291, 571], and is effective in adolescents [61, 224, 356, 1127, 604] and in patients with weight regain post-bariatric surgery [206, 261, 464, 526, 610, 624, 1222]. Tirzepatide generally shows superior weight loss compared to semaglutide [56, 167, 201,

203, 209, 272, 345, 407, 426, 449, 484, 554, 581, 583].

- **Glycemic Control:** Semaglutide significantly improves HbA1c levels, often by 0.9-1.6% [81, 83, 87, 118, 157, 1707, 1415, 1434, 184, 255, 306, 312, 326, 328, 332, 395, 482, 495, 512, 519, 556, 589, 594, 602, 605, 771, 969, 1052, 1170, 1191], and reverses prediabetes to normoglycemia [33, 239, 183]. It also reduces insulin dose in T1D patients [24, 29, 52, 495].
- **Cardiovascular and Renal Benefits:** Semaglutide consistently reduces major adverse cardiovascular events (MACE) by 14-28% [8, 21, 64, 66, 69, 107, 109, 130, 141, 1713, 1741, 198, 205, 219, 233, 300, 325, 348, 384, 386, 397, 413, 416, 442, 497, 503, 535, 546, 549, 550, 568, 573, 763], cardiovascular mortality by 16-23% [66, 109, 481, 535, 643, 895], and heart failure hospitalizations [27, 367, 369, 397, 416, 1004, 1087] and symptoms in obese HFpEF patients [178, 308, 379, 479, 497, 631, 689]. It also reduces the risk of chronic kidney disease (CKD) progression, end-stage renal disease (ESRD), and albuminuria [47, 66, 124, 316, 325, 349, 563, 817, 955, 688].
- **Hepatic Health:** Semaglutide improves MASLD/MASH resolution and liver fibrosis [2, 49, 73, 105, 123, 127, 148, 152, 1567, 202, 220, 243, 247, 259, 324, 328, 352, 434, 439, 499, 507, 521, 621, 921, 942], reducing hepatic triglycerides, steatosis, and liver injury markers [2, 49, 170, 259, 281, 352, 376, 434, 499, 507, 521, 621, 921, 942, 1145, 1521].
- **Neurological and Cognitive Effects:** Semaglutide shows neuroprotective effects, attenuating Alzheimer's disease progression [115, 231, 553], improving cognitive function in T2DM [221, 225, 377, 430, 460, 468, 553, 588], and potentially in people with HIV (PWH) [155, 440]. It is also being investigated for Parkinson's disease [17, 257, 578] and opioid use disorder [116], and reduces alcohol intake [68, 172, 436, 616, 974].
- **Adverse Events and Safety Profile:** Common adverse events (AEs) include gastrointestinal issues (nausea, vomiting, diarrhea, constipation) [64, 78, 111, 113, 319, 343, 490, 482, 615, 617, 623, 624, 635, 1199, 1751, 1404], which can impact adherence [263, 482, 492]. There are reported associations with non-arteritic anterior ischemic optic neuropathy (NAION) [23, 187, 207, 475, 476, 557, 580, 575, 603, 620, 638, 826], thyroid cancer risk [590], and muscle loss/functional decline in older adults [265, 362, 199]. Some studies suggest increased risk of surgical complications like pseudoarthrosis [453, 477, 552, 576] and residual gastric content pre-surgery [22, 350, 368, 487, 1404]. Psychiatric AEs like depression and suicidal ideation have been reported in pharmacovigilance studies [353, 372, 414, 619], though cohort studies show lower risk [1169, 452].
- **Formulation and Delivery:** Semaglutide is available in subcutaneous and oral formulations, with subcutaneous generally showing greater weight loss and some metabolic benefits [6, 771, 640, 969], though oral formulations are effective for glycemic control and cardiovascular protection [8, 83, 1525, 1751, 300, 319, 395, 406, 416, 522, 546, 550, 594, 605, 612, 643]. Novel delivery systems are being developed to enhance oral bioavailability [121, 149, 162, 186, 194, 235, 268, 419, 432, 587, 639, 645].

- **Cost-effectiveness and Access:** Semaglutide is considered cost-effective for T2DM and obesity management in various healthcare settings [26, 105, 154, 502, 572, 1054, 1530, 1721], but access disparities exist due to cost, insurance, and service capacity [20, 46, 228, 251, 285, 598, 1412].

5) Discussion

5.1 Principal finding

The principal finding of this review is that semaglutide treatment for obesity or overweight without type 2 diabetes is associated with a median body weight reduction of 15.3% (range: 13.4% to 19.5%) over approximately one year [98, 107, 1147, 567, 318, 319, 333, 283, 455, 484, 209, 272]. This represents a clinically significant weight loss that can profoundly impact health outcomes.

5.2 Clinical implications

- **Obesity and T2DM Management:** Semaglutide is a highly effective agent for weight loss and glycemic control across diverse populations, including adolescents and those with complex comorbidities like T1D or after bariatric surgery [61, 224, 328, 464].
- **Cardio-renal Protection:** Its robust benefits in reducing major adverse cardiovascular events (MACE), cardiovascular mortality, and progression of chronic kidney disease (CKD) position it as a cornerstone therapy for patients with T2DM and associated risks [8, 21, 66, 109, 325, 546, 895].
- **Beyond Metabolic Syndrome:** Emerging evidence suggests therapeutic potential in neurological conditions such as Alzheimer's and Parkinson's disease, and even for reducing alcohol consumption, expanding its clinical utility [115, 17, 68, 172, 974].
- **Patient Monitoring:** Clinicians should be aware of common gastrointestinal adverse events and rare but serious concerns like non-arteritic anterior ischemic optic neuropathy (NAION) and potential surgical complications, necessitating careful patient selection and monitoring [78, 207, 350, 477, 557].
- **Personalized Approach:** Response to semaglutide can vary based on genetic factors, baseline characteristics, and adherence, highlighting the importance of personalized treatment strategies and patient engagement for optimal outcomes [339, 474, 537, 544].

5.3 Research implications / key gaps

- **Long-term Safety in Diverse Cohorts:** Further long-term studies are needed to fully characterize rare adverse events, particularly ocular and surgical risks, across broader

patient demographics, including those with specific predispositions [187, 477, 552].

- **Mechanisms Beyond Weight Loss:** Research should continue to elucidate the precise molecular mechanisms underlying semaglutide's benefits in non-metabolic conditions (e.g., neuroprotection, anti-inflammatory effects) to identify new therapeutic targets [115, 243, 321, 377, 553].
- **Optimal Combination Therapies:** Head-to-head trials and real-world studies are needed to define optimal combination strategies with other agents (e.g., SGLT2 inhibitors, novel dual/triple agonists) to maximize benefits and minimize side effects [123, 158, 173, 232, 366, 385, 404, 595].
- **Accessibility and Health Equity:** Studies are required to address socioeconomic and racial disparities in access to semaglutide and evaluate interventions to ensure equitable distribution and utilization [20, 46, 228, 598].
- **Impact on Body Composition:** More detailed studies are needed to precisely quantify the impact of semaglutide on lean body mass preservation versus fat mass reduction across various populations and treatment durations [166, 199, 291, 362, 571, 1036].

5.4 Limitations

- **Heterogeneity of Study Designs** — The review incorporates mixed study designs (RCTs, cohorts, experimental), which affects the overall strength of evidence and comparability of results.
- **Variability in Follow-up Durations** — Follow-up periods range from weeks to several years, limiting direct comparisons for long-term outcomes and safety profiles across all studies.
- **Focus on Specific Populations** — Many studies target specific patient groups (e.g., T2DM, obesity, CKD), which may limit the generalizability of findings to broader populations.
- **Reporting Bias in Observational Data** — Retrospective cohort studies and pharmacovigilance reports are susceptible to reporting biases, which can influence the perceived incidence of adverse events.
- **Lack of Direct Head-to-Head Comparisons** — While some studies compare semaglutide to other agents, a definitive network of direct comparisons for all relevant outcomes is not universally available, especially for newer dual/triple agonists.

5.5 Future directions

- **Robust Real-World Evidence** — Conduct large, prospective, real-world studies to confirm long-term safety and effectiveness in diverse, unselected populations.
- **Mechanistic Pathway Elucidation** — Investigate the precise molecular pathways of semaglutide's action in non-metabolic conditions using advanced omics technologies.
- **Comparative Effectiveness Research** — Perform head-to-head trials comparing semaglutide with emerging multi-agonist therapies across a comprehensive range of outcomes.
- **Health Economic Impact Assessment** — Evaluate the long-term cost-effectiveness and societal impact of widespread semaglutide use, considering access and equity.
- **Biomarker Identification for Response** — Identify predictive biomarkers for treatment response and adverse events to enable personalized therapeutic approaches.

6) Conclusion

Semaglutide treatment for obesity or overweight without type 2 diabetes is associated with a median body weight reduction of 15.3% (range: 13.4% to 19.5%) over approximately one year [98, 107, 1147, 567, 318, 319, 333, 283, 455, 484, 209, 272]. This efficacy extends to significant improvements in glycemic control, cardiovascular, renal, and hepatic health, and shows promising neuroprotective effects across various patient populations. However, the heterogeneity of study designs and variability in follow-up durations remains the most significant limitation affecting the certainty of some conclusions. Clinicians should consider semaglutide as a powerful tool for comprehensive metabolic and cardiovascular risk reduction, while diligently monitoring for known and emerging adverse events.

References

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Figure 1. Publication-year distribution of included originals

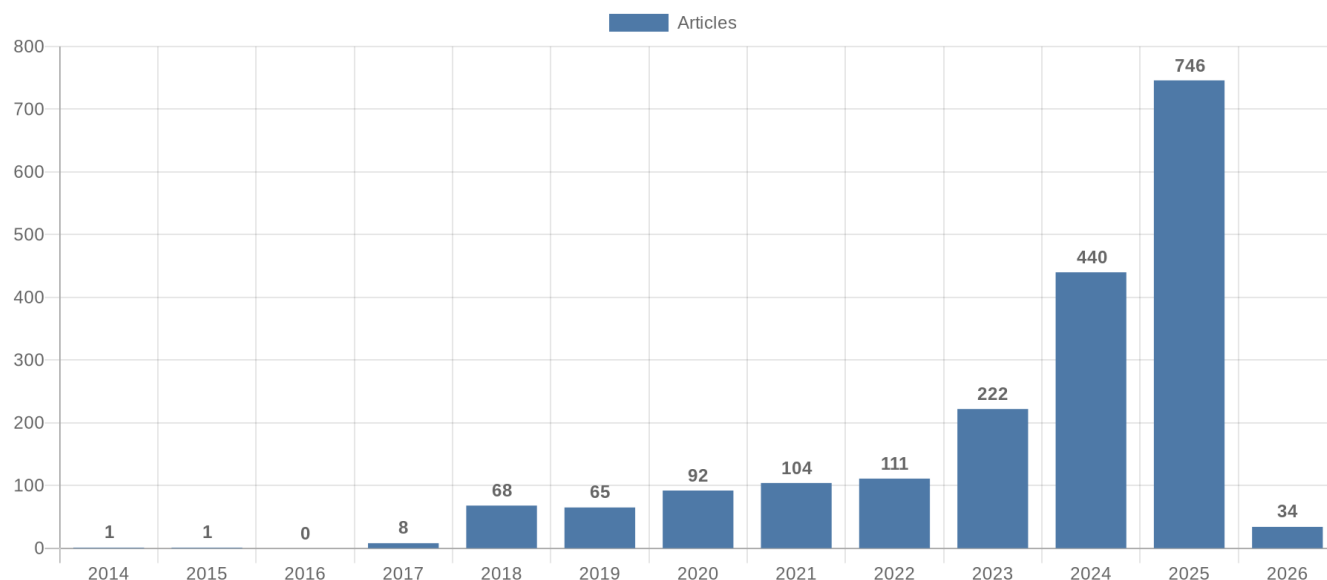


Figure 2. Study-design distribution of included originals

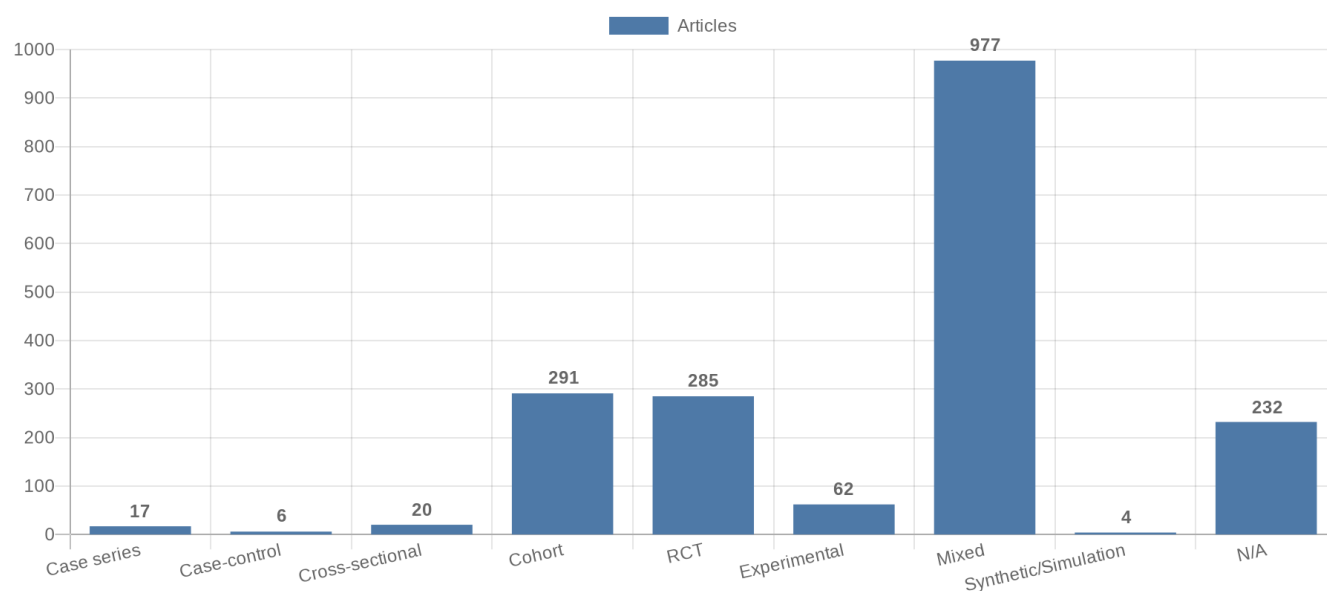


Figure 3. Study-type (directionality) distribution of included originals

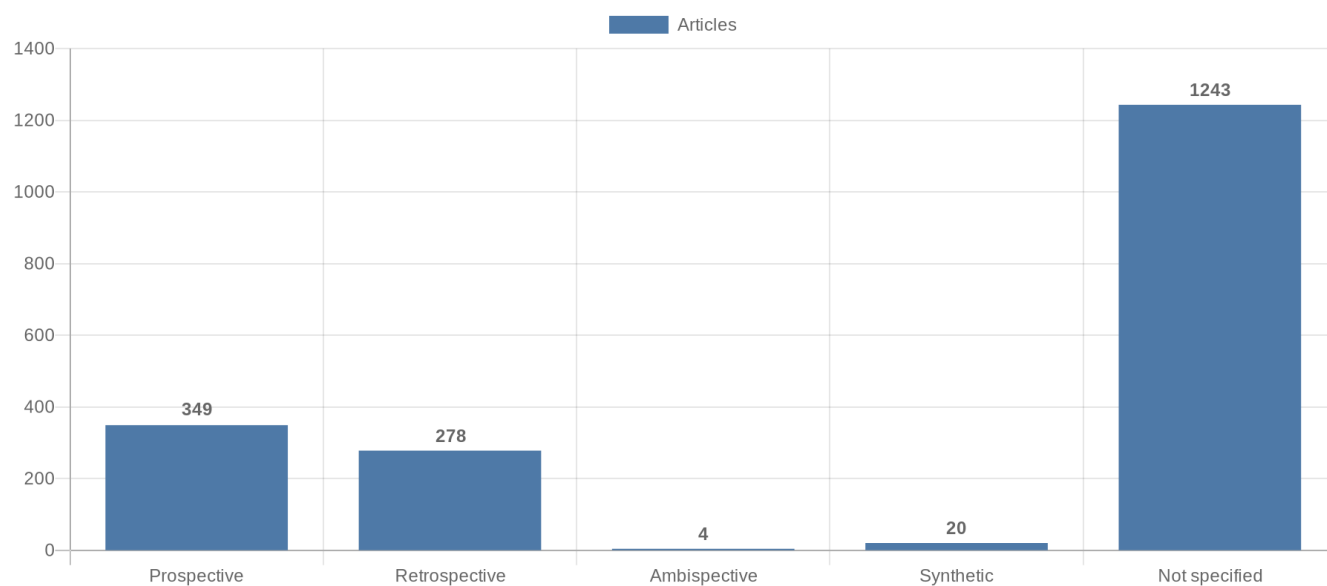


Figure 4. Main extracted research topics

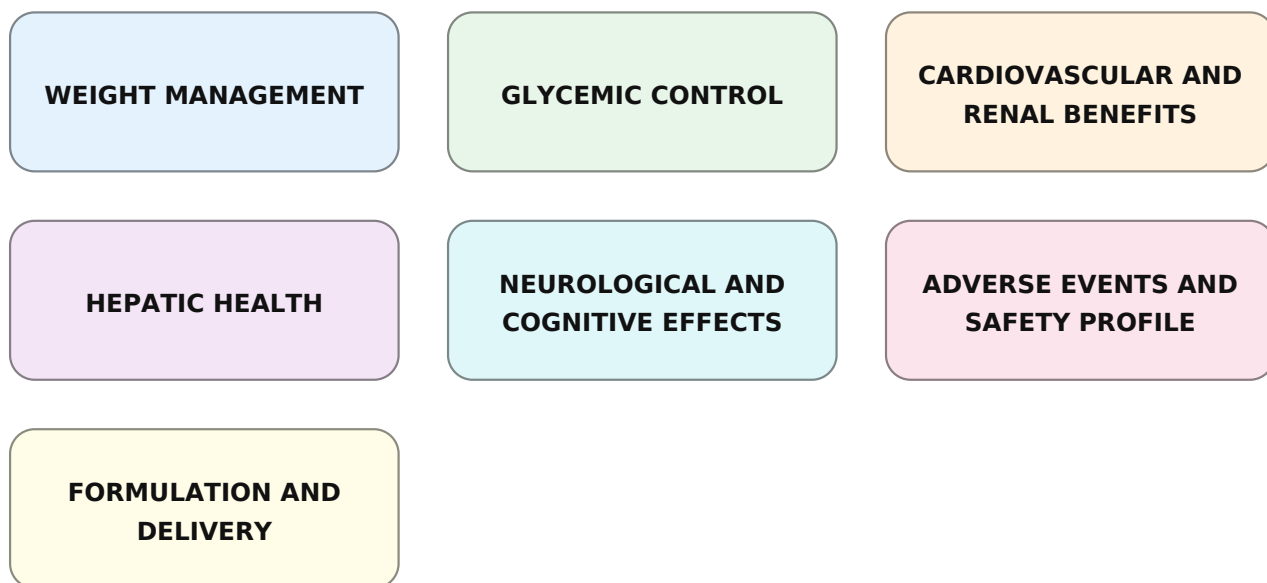


Figure 5. Limitations of current studies (topics)

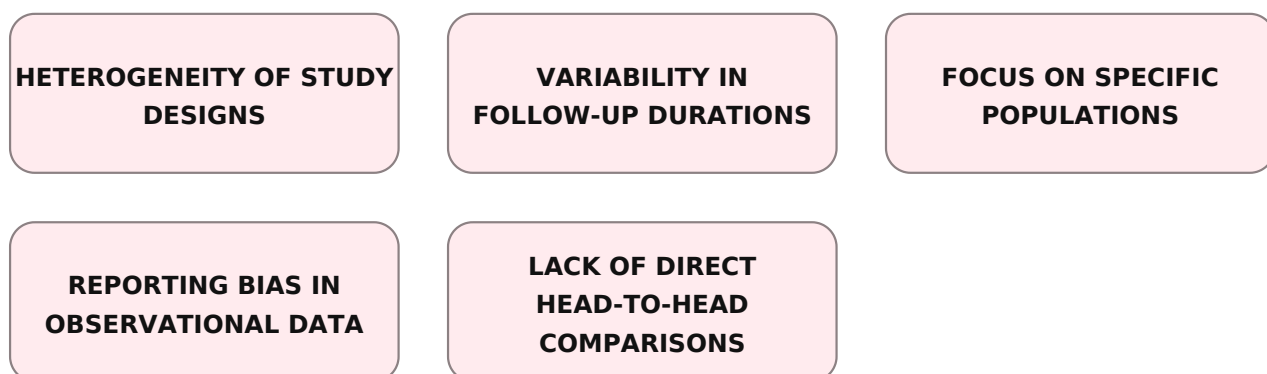


Figure 6. Future research directions (topics)

