Received: 29 September 2023 | Revised: 13 February 2024 | Accepted: 19 February 2024

DOI: 10.1111/ijpo.13113

REVIEW ARTICLE

Pediatric OBESITY WILEY

Pharmacological interventions for the management of children and adolescents living with obesity—An update of a Cochrane systematic review with meta-analyses

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Summary

Importance: The effectiveness of anti-obesity medications for children and adolescents is unclear.

Objective: To update the evidence on the benefits and harms of anti-obesity medication.

Data Sources: Cochrane CENTRAL, MEDLINE, ClinicalTrials.gov and WHO ICTRP (1/1/16–17/3/23).

Study Selection: Randomized controlled trials ≥6 months in people <19 years living with obesity.

Data Extraction and Synthesis: Screening, data extraction and quality assessment conducted in duplicate, independently.

Main Outcomes and Measures: Body mass index (BMI): 95th percentile BMI, adverse events and quality of life.

Results: Thirty-five trials ($N = 4331$), follow-up: 6–24 months; age: 8.8–16.3 years; BMI: 26.2–41.7 kg/m^2. Moderate certainty evidence demonstrated a −1.71 (95% confidence interval [CI]: −2.27 to −1.14)-unit BMI reduction, ranging from −0.8 to −5.9 units between individual drugs with semaglutide producing the largest

reduction of −5.88 kg/m^2 (95% CI: −6.99 to −4.77, $N = 201$). Drug type explained ~44% of heterogeneity. Low certainty evidence demonstrated reduction in 95th percentile BMI: −11.88 percentage points (95% CI: −18.43 to −5.30, $N = 668$). Serious adverse events and study discontinuation due to adverse events did not differ between medications and comparators, but medication dose adjustments were higher compared to comparator (10.6% vs 1.7%; RR = 3.74 [95% CI: 1.51 to 9.26], $I^2 = 15\%$), regardless of approval status. There was a trend towards improved quality of life. Evidence gaps exist for children, psychosocial outcomes, comorbidities and weight loss maintenance.

Conclusions and Relevance: Anti-obesity medications in addition to behaviour change improve BMI but may require dose adjustment, with 1 in 100 adolescents experiencing a serious adverse event.

KEYWORDS
adolescents, adverse events, anti-obesity medication, body mass index, meta-analysis, obesity

1 | INTRODUCTION

Obesity is a major public health concern with increasing incidence and prevalence over the last four decades worldwide.[1–3] Between 1.0% and 5.5% of children and adolescents are living with severe obesity, which is often accompanied by comorbidities, such as type 2 diabetes mellitus (T2DM) and psychological comorbidities.[4–6]

Obesity in childhood often transitions into adulthood, indicating the chronic nature of the disease and emphasizing the need for comprehensive, effective and safe treatment.[7–9] As a first-line treatment, guidelines recommend multimodal behaviour-changing interventions, focusing on improving diet and increasing physical activity, for children and adolescents living with obesity; however, the impact of these interventions on body weight status is limited.[10,11] For children and adolescents with unsuccessful attempts to reduce body weight status, or with more severe comorbidities or severe obesity, further treatment approaches, such as anti-obesity medication, are recommended.[11]

A Cochrane systematic review published in 2016 included 21 randomized controlled trials (RCTs) of drug plus behaviour change and showed a reduction in BMI of −1.3 kg/m^2 (95% CI: −1.9 to −0.8).[12] However, the rapid development, testing and approval of new anti-obesity medications, such as glucagon-like peptide 1 receptor agonists (GLP-1-RA) and phentermine/topiramate, require a timely update of the evidence base. Therefore, we conducted an update of the Cochrane review published by Mead et al.[12] to review published evidence up to March 2023; we also broadened the outcomes of interest to include psychological comorbidities and assessed the certainty of evidence.[13]

2 | METHODS

The methods are underpinned by the methods in the Cochrane Handbook for Systematic Reviews of Interventions[14] and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)-2020 statement and its extensions.[15,16] The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO 2022 CRD42022376529). We followed the methods of the Cochrane review[12] but broadened the outcomes of interest and assessed the certainty of evidence using current guidance by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[13] The outcomes of interest were broadened and informed by recent evidence on patient-reported outcomes in order to reflect a person-centred approach, which focusses on the needs of children and adolescents living with obesity.[17–19]

2.1 | Data sources and searches

All studies included in the Cochrane review[12] were carried forward. In March 2023, a search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform to capture studies published from 1 January 2016 to 17 March 2023. An experienced information specialist (MIM) built on the search strategies of the Cochrane review[12] by adding terms for drugs developed since 2016 (eMethods in Supplement). Additional citations were identified through review of reference lists of included RCTs, key review articles published since 2016 and literature suggested by co-authors and their contacts.

2.2 | Study selection

Two reviewers independently screened titles/abstracts and full-text articles to determine eligibility (reviewers included AG, GT, JM and TB) using a prespecified criterion (eTable 1 in Supplement). Conflicts

were resolved by consensus or referred to a third reviewer (TB) to resolve conflicts. In brief, the review included RCTs of young people living with obesity aged <19 years. Interventions included any anti-obesity medication, which aimed to treat paediatric obesity, regardless of regulatory approval for obesity treatment in youth <18 years by agency or agencies appropriate to site(s) of study. The intervention had to be ≥12-weeks with a minimum of 6-month follow-up from baseline. Comparators could be placebo, usual care and/or other therapies including surgical interventions. Concomitant therapies such as diet and exercise were required to be the same in both the intervention and comparator groups. There were no limits on language, setting or country.

2.3 | Data extraction and quality assessment

One reviewer extracted data, which were verified by another reviewer for completeness and accuracy (reviewers included AG, GT, JM and TB). Differences were resolved by consensus or referred to a third reviewer (TB) to resolve conflicts. Data previously extracted and input into meta-analyses in the Cochrane review[12] were exported via Review Manager software into Excel and combined with data from the new studies. All publications of trials included in the Cochrane review[12] were checked for additional outcomes relevant to the review (as per the widened scope; see section 'Data Synthesis and Analysis'). One reviewer assessed risk of bias (RoB) of each new included study using the Cochrane RoB tool that had been used in the Cochrane review[12] (eTable 2 in Supplement) and a second reviewer verified the assessments.[20]

2.4 | Data synthesis and analysis

BMI was defined as a primary outcome in the Cochrane review[12] and was the most reported outcome. We did not exclude any of the outcomes from the Cochrane review; we were aware of the need to present more than one continuous BMI metric[21] and selected additional outcomes based on evidence from studies that investigated the importance of outcomes according to adolescents living with obesity, healthcare providers and physicians.[17–19,22] For each outcome category, three senior reviewers (LJE, ASK and DW) voted for their preferred choices of outcomes. From the most frequently preferred outcomes, seven outcomes were chosen for the Table 2, which was used to present the certainty of the evidence for BMI, BMI as percentage of 95th percentile (new), serious adverse events, health-related quality of life (HRQoL), T2DM (new), social functioning (new) and self-esteem.[23,24] One reviewer (TB) assessed the certainty of evidence using GRADE, which was checked by a second reviewer (AJ and GT), and the gradings were discussed with all co-authors.[13] In addition, we further analysed the following adverse event outcomes: dosage adjustment due to adverse events and trial discontinuation due to adverse events.

One author (AJ) conducted all statistical analyses in discussion with all other authors. The mean difference effect size (mean intervention vs mean placebo) was used as the primary effect size for continuous outcomes and risk ratios for binary outcomes. Analyses using standardized mean difference allowing for the inclusion of multiple quality of life indicators are reported in supplementary materials. In the meta-analysis, we reported outcomes at end of drug treatment phase and the vast majority of trials continued medication until final measurement. Random effects meta-analysis was conducted with a restricted maximum likelihood estimator using RStudio running the 'metafor', 'meta' and 'RoBMA' packages. Subgroup analyses and/or meta-regression were carried out to explore any heterogeneity (indicated by I^2 >0). For the primary outcome (BMI), we subgrouped by drug, age (<12 vs. 12+), treatment length (<6 months vs. 6 months+), study (in original review vs newly identified) and risk of bias (low risk vs unclear/high risk). As stated in the protocol, we included all drugs that have been studied in RCTs in paediatric obesity populations, irrespective of their current regulatory approval status. Additional post hoc analyses was undertaken, subgrouping drugs according to drugs approved by at least one agency and licenced to treat paediatric obesity in this population, drugs used off-label and drugs that have been withdrawn. Meta-regressions examined the association between percentage of females in the intervention group and effect size. Full reporting of moderation analysis can be found in eMethods in Supplement.

Several bias detection methods were carried out including Egger's regression test, tests of excess significance, trim and fill, and graphical display of study heterogeneity.[25–28] Finally, a Bayesian meta-analysis was conducted to examine the strength of evidence for the presence of an effect, the presence of heterogeneity and the presence of publication bias.[29] All data and analysis scripts can be found at https://osf.io/gr4hx/.

3 | RESULTS

The update searches identified 1287 records, of which 14 new RCTs[30–43] (41 records) were included and combined with 21 RCTs[44–64] (33 records) from the Cochrane review,[12] making a total of 35 RCTs. Of the 35 included trials, two were identified from trial registry searches alone and are terminated trials (NCT02273804 and NCT03338296).[30,31] Another two examined the effect of pharmacotherapy for weight maintenance following weight reduction, and we report the data narratively.[33,41] Searches in trial registries identified 10 ongoing RCTs (eMethods in Supplement). Further information is available on study flow (eFigure 1 in Supplement), exclusion of full-text articles and unpublished or ongoing RCTs (eMethods in Supplement).

Table 1 summarizes the main characteristics of included trials. Of the 35 included trials, 12 were conducted in the USA, 2 each in Brazil, Canada, the Netherlands, Spain and Turkey, and one each in Australia, Chile, China, Iran, Mexico, Sri Lanka, Sweden, France and the UK. Five

TABLE 1 Characteristics of randomized controlled trials.

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
Atabek[44] Turkey, NR	**Metformin:** oral, twice daily, 500 mg × 2 (1 g)/d, 6 months **Placebo:** oral, twice daily, 2 tablets/d, 6 months **Diet and physical activity advice:** individual consultation sessions with a nutritionist, completed food diary at beginning and end of trial, advised to perform 30 min of aerobic physical activity per day, 6 months	**Metformin:** 50; 11.8 (2.8); NR; 28.5 (3.4); 100 hyperinsulinemia; **Placebo:** 50; 11.6 (2.7); NR; 28.0 (3.4); 100 hyperinsulinemia
Bassols[37] Spain, N	**Metformin:** oral, once daily, 850 mg/d, 'at dinner time', 24 months **Placebo:** oral, once daily, 'at dinner time', 24 months **Co-intervention:** none	**Metformin:** 33; 8.8 (SE 0.6); Caucasian 100; NR; fasting insulin levels >6 mIU/L; visceral-to-subcutaneous fat ratio (MRI >90th centile) **Placebo:** 44; 10.0 (SE 0.5); Caucasian 100; NR; fasting insulin levels >6 mIU/L; visceral-to-subcutaneous fat ratio (MRI >90th centile)
Berkowitz[46] USA, Y	**Sibutramine:** oral, 1 dose/d, placebo (week 1) 5 mg/d sibutramine (week 2) 10 mg/d (weeks 3–6) 15 mg/d (week 7 to month 6), 6 months (plus an open-label phase for additional 6 months) **Placebo:** oral, 1 dose per day, (months 1–6), 6 months **Behavioural program:** in phase 1 (drug–placebo phase), participants attended 13 weekly group sessions, while in phase 2 (drug, open label), group sessions were held biweekly then monthly. Parents met separately from participants. Instructed to consume 1200 to 1500 kcal/d and to engage in 120 min of walking or similar activity per week. Eating and activity logs kept daily for 12 months	**Sibutramine:** 72; 14.1 (1.3); White 49, Black 49, other 2; 37.5 (4.0); NR **Placebo:** 62; 14.1 (1.2); White 62, Black 33, other 5; 38.0 (3.6); NR
Berkowitz[45] USA, Y	**Sibutramine:** oral, 1 dose per day, 10 mg/d (baseline to month 6), 15 mg/d from month 6 in participants who had not lost more than 10% of their initial BMI, 12 months **Placebo:** oral, 1 dose per day, placebo (baseline to month 6), up titrated after 6 months in participants who had not lost more than 10% of their initial BMI, 12 months **Behavioural therapy:** each individual centre implemented flexible lifestyle modification approaches that were specific to participants' needs. This included self-monitoring of eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring and social support. Participants were given counselling at each visit and nutritional counselling, 12 months	**Sibutramine:** 66; 13.6 (1.3); White 56, African American 22, Hispanic or Mexican American 16, other 6; 35.9 (4.1); 50.5 dyslipidaemia, 1.4 hypertension **Placebo:** 62; 13.7 (1.3); White 59, African American 19, Hispanic or Mexican American 14, other 9; 36.1 (3.8); 57.4 dyslipidaemia, 2.3 hypertension
Chanoine[47] USA and Canada, Y	**Orlistat:** oral, dose 3 times per day, 120 mg × 3 (360 mg)/d, 1 year **Placebo:** oral, dose 3 times per day, 1 year **Behavioural therapy:** participants were prescribed a nutritionally balanced, hypocaloric diet and at each trial visit the dietitian spoke about compliance. Behavioural modification involved techniques to limit calorie and fat intake, eating more slowly, avoiding snacks and avoiding overeating. Guidelines were given to encourage regular physical activity and reduce sedentary behaviour; compliance was monitored by a behavioural psychologist at each visit. Length = 54 weeks	**Orlistat:** 65; 13.6 (1.3); White 75, Black 19, Other 6; 35.7 (4.2); 25% metabolic syndrome, $n = 8$ fatty liver infiltration/hepatomegaly, $n = 3$ gallstones **Placebo:** 71; 13.5 (1.2); White 78, Black 14, Other 8; 35.4 (4.1); NR

TABLE 1 (Continued)

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
Clarson[48] Canada, N	**Metformin:** oral, 3 times daily, 500 mg × 3 (1.5 g), 6 months **No placebo** comparator **Behaviour change:** monthly individual visits and 2 group sessions. Fitness specialist supervised participants in an individual 30-min exercise sessions every 2 months. Diet advice and physical activity advice given. Progress monitored by weekly telephone calls and monthly visits. 6 months	**Metformin:** NR; 13.1 (10.1–16.1); NR; 36.4 (SE 1.8); 100 insulin resistant, HOMA >3.0 **No placebo** comparator: NR; 13.1 (10.1–16.1); NR; 33.9 (SE 1.1); 100 insulin resistant, HOMA >3.0
Clarson[32] Canada, N	**Metformin:** extended release, oral, start taking once daily, 500 mg/d increase by 500 mg/d every 7 days to maximum tolerated dose 2000 mg/d, taken before evening meal, 2 yr **Placebo:** oral, once daily, 10 mg, 2 yr **Co-intervention:** 12 weekly group behaviour change sessions based on the group-mediated cognitive-behavioural intervention model. Randomized to engage in moderate or vigorous intensity supervised exercise program for first 12 weeks and then weekly supervised group exercise (moderate and vigorous groups combined) at a Community Centre and received 2-year membership. Treatment sessions with a dietitian and social worker monthly for the first year and then every 3 months for the second year.	**Metformin + moderate exercise:** 41.2; 13.4 (2.1); Caucasian 82, Asian 6, native 6, other 6; 31.6 (5.2); none **Metformin + vigorous exercise:** 62.5; 13.9 (2.4); Caucasian 81, native 6, other 13; 34.4 (5.7); none **Placebo + moderate exercise:** 61.1; 14.3 (2.0); Caucasian 78, Black 11, native 6, other 6; 32.0 (5.1); none **Placebo + vigorous exercise:** 66.7; 13.3 (2.2); Caucasian 67, Asian 6, other 28; 32.2 (6.3); none
Fox[33] USA, Y	**Topiramate:** oral, once daily in the evening, 75 mg/d, 24 weeks. Topiramate was initiated at a dose of 25 mg once daily in the evening, escalated to 50 mg once daily in the evening after 1 week, and further escalated to 75 mg/d after 2 weeks (25 mg in the morning and 50 mg in the evening), 24 weeks. **Placebo:** oral, twice daily, 24 weeks **Co-intervention:** before randomization all participants received 4 weeks of meal replacement therapy (free of charge to participants), total caloric intake 1400 kcals/d. Participants were encouraged (but not required) to meet a goal of at least 5% BMI reduction during the meal replacement phase. Dietary and physical activity behaviour change counselling was provided on the transition from meal replacements (initial 4 weeks) to regular dietary habits, for 24 weeks.	**Topiramate:** 62.5; 14.9 (1.6); White: 62.5 African American/Black 18.8, other 18.8; 41.0 (5.0); none **Placebo:** 64.3; 15.7 (1.8); White 57, African American/Black 7, other 36; 39.5 (4.0); none
Fox[41] USA, Y	**Exenatide:** extended release, subcutaneous injection, once weekly, 2 mg/week, 52 weeks **Placebo:** subcutaneous injection, once weekly, 52 weeks **Co-intervention:** before randomization all participants received 4–8 weeks of meal replacement therapy (free of charge to participants), total caloric intake 1400 kcals/d. Participants who achieved ≥5% BMI reduction were then randomized. Dietary and physical activity behaviour change counselling, monthly, 52 weeks.	**Exenatide:** 55; 15.9 (1.6); Non-Hispanic 82 Hispanic 15, White 79, Black 9, Asian 0, American Indian 0, Multiple 9, Missing 3, Other 0; 36.5 (4.3); none **Placebo:** 41; 16.1 (1.5); Non-Hispanic 94, Hispanic 6, White 85, Black 6, Asian 0, American Indian 0, Multiple 6, Missing 3, Other 0; 37.3 (4.6); none
Franco[49] Brazil, N	**Sibutramine:** oral, once daily, 10 mg, 6 months **Placebo:** oral, once daily, 10 mg, 6 months **Dietary guidance:** the dietary guideline proposal was of a low-calorie diet with restriction of 25% of the total recommended calories for a teenager	**Sibutramine:** 56; 13.3 (1.8); NR; 33.9 (7.2); NR **Placebo:** 56; 12.3 (1.7); NR; 32.8 (5.8); NR

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TABLE 1 (Continued)

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
Freemark[50] USA, Y	**Metformin:** oral, 2 doses per day, 500 mg × 2 (1 g)/d, 6 months **Placebo:** oral, 2 doses per day, 6 months **Co-intervention:** none	**Metformin:** 79; 14.4 (0.6); White 64, Black 36; 41.5 (0.9); 100 fasting hyperinsulinemia and at least one first- or second-degree relative with T2DM **Placebo: 46; 15.4 (0.5);** White 47, Black 53; 38.7 (1.3); 100 fasting hyperinsulinemia and at least one first- or second-degree relative with T2DM
Garcia-Morales[51] Mexico, Y	**Sibutramine:** oral, 1 dose per day, 10 mg/d, 6 months **Placebo:** oral, 1 dose per day, 6 months **Diet + exercise:** diet and exercise advice was tailored to each participant. Advice was given on recommended food portions and possible combinations, and all participants were advised to perform at least 30 min of aerobic physical activity per day. Each participant also attended individual consultation sessions with a registered paediatric nutritionist. A detailed food consumption questionnaire was completed at the beginning and end of trial medication period. Length = 6 months	**Sibutramine:** 61; 15.2 (1.3); NR; 35.1 (5.3); 8.7 high blood pressure, 8.7 high glucose, 43.5 high triglycerides, 8.7 high cholesterol, 4.3 high LDL, 13 high HDL **Placebo:** 52; 14.7 (1.1); NR; 36.6 (5.2); 30.4 high blood pressure, 8.7 high glucose, 52.2 high triglycerides, 34.8 high cholesterol, 17.4 high LDL
Godoy-Matos[52] Brazil, Y	**Sibutramine:** oral, 1 dose per day, 10 mg/d, 6 months **Placebo:** oral, 1 dose per day, 6 months **Hypocaloric diet + exercise:** participants were given dietary counselling to achieve an energy deficit of 500 kcal/d at the start of the run-in phase (no further visits after). Physical activity instructions were delivered by the attendant doctors in a brief written protocol aimed to obtain mainly aerobic moderate exercises for at least 30 min/d. A lifestyle intervention was not given during 6-month trial	**Sibutramine:** 83; female 15.9 (1.1), male 16.7 (0.6); NR; female 37.5 (3.8), male 37.6 (4.3); NR **Placebo:** 80; female 16.3 (1.2), male 16.7 (0.6); NR; female 35.8 (4.2), male 37.4 (1.9); NR
Kelly[39] Belgium, Mexico, Russia, Sweden, USA; Y	**Liraglutide:** subcutaneously, once daily, 3 mg/d, 56 weeks. Initial dose 0.6 mg/d for 1 week, increased weekly until maximum tolerated dose or 3.0 mg/d **Placebo:** subcutaneously, once daily, 3 mg/d, 56 weeks **Co-intervention:** counselling about healthy nutrition and physical activity for weight loss, 82 weeks	**Liraglutide:** 56.8; 14.6 (1.6); Hispanic 25.6, White 84, Black 11, Asian 2, American Indian or Alaska Native 0, other 3; 35.3 (5.1); 25.6 dysglycemia **Placebo:** 61.9; 14.5 (1.6); Hispanic 19, White 91, Black 5, Asian 0, American Indian or Alaska Native 1, Other 3; 35.8 (5.7); 26.2 dysglycemia
Kelly[42] USA, Y	**Phentermine/topiramate**, 7.5 mg/ 46 mg/d, orally once daily in the morning, 56 weeks **Phentermine/topiramate**, 15 mg/ 92 mg/d, orally once daily in the morning, 56 weeks **Placebo:** oral once daily in the morning **Co-intervention:** 500-kilocalorie/d deficit and family-based lifestyle modification program that included physical activity, behaviour change, and family support (5–15 min each visit).	**Phentermine/topiramate mid-dose:** 51.9; 14.1 (1.3); Hispanic or Latino 46, White 67; Black/African American 26; Other 7, American Indian or Alaska Native 0, Asian 0, Native Hawaiian or other Pacific Islander 0; 36.9 (6.8); none **Phentermine/topiramate top dose:** 55.8; 13.9 (1.4); Hispanic or Latino 30, White 63, Black/African American 32, other 4, American Indian or Alaska Native 1, Asian 1, Native Hawaiian or other Pacific Islander 0; 39.0 (7.4); none **Placebo:** 53.6; 14.0 (1.4); Hispanic or Latino 23, White 75, Black/African American 18, Other 7, American Indian or Alaska Native 0, Asian 0, Native Hawaiian or other Pacific Islander 0; 36.4 (6.4); none
Kendall[53] UK, N	**Metformin:** oral, twice daily, 500 mg × 2 + 500 mg (1.5 g), 6 months **Placebo:** oral, twice daily, 2 + 1 (3) tablets/d, 6 months **Healthy lifestyle advice:** participants provided with a standardized healthy lifestyle advice at the start in a 1-to-1 sessions, including a healthy diet advice sheet and increased levels of exercise (available upon request). A lifestyle intervention was not given during the 6-month trial	**Metformin:** 66; 13.7 (2.3); White 80, Asian 19, Afro-Caribbean 11; 37.1 (6.4); 100 hyperinsulinemia or IGT **Placebo:** 69; 13.6 (2.2); White 72, Asian 26, Afro-Caribbean 1; 36.0 (6.3); 100 hyperinsulinemia or IGT

TABLE 1 (Continued)

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
Li[38] China, NR	**Metformin:** oral, ≤8 yr = 0.25 g/3 times daily, children >8 yr = 0.5 g 3 times daily, half an hour before meals, 6 months **No placebo** comparator **Co-intervention:** maintain a light diet and healthy recipes were formulated. Caloric intake 10–14 yr was 1000–1200 kcal/d; advice on changing eating habits, including chewing carefully and slowly and avoiding distractions during eating; >30 min/d exercise. Length = 6 months	**Metformin:** 38; 12.3 (1.6); NR; 31.8 (2.5); 100 hyperinsulinemia **No placebo** comparator: 33; 12.0 (1.5); NR; 30.8 (2.5); 100 hyperinsulinemia
Maahs[54] USA, N	**Orlistat:** oral, 3 doses per day, 120 mg × 3 (360 mg)/d, 6 months **Placebo:** oral, 3 doses per day, 6 months **Diet + exercise therapy:** the goal caloric intake was calculated using the Harris–Benedict equation with ambulating activity factor (500 calories was subtracted from the final number to obtain daily calorie level). Participants were instructed to increase activity using a paediatric activity pyramid and encouraged to exercise for at least 30 min, 3 times per week. Monthly follow-up visits with a dietitian reinforced this advice. Log sheets and diet records were also completed. Length = 6 months	**Orlistat:** 60; 15.8 (1.5); Hispanic 60; 39.2 (5.3); NR **Placebo:** 75; 15.8 (1.4); Hispanic 65; 41.7 (5.0); NR
Mauras[55] USA, N	**Metformin:** oral, twice daily, 500 or 1000 mg (dependent on age), 6 months **No placebo comparator** **Diet + exercise intervention:** dietary counselling provided with recommended decrease of 250 calories/d to 500 calories/d. Intense follow-up provided by dietitian. Participants given free membership to YMCA or gym. Encouraged to exercise at least 3 times per week for 30 min per sessions. Activity diary kept and pedometer worn. Length = 6 months	**Metformin:** 57; 12.3 (0.5); White 51, African American 37, Other 11; 32 (1); 100 normal glucose tolerance and elevated hsCRP and/or fibrinogen concentrations >2 SDs **No placebo comparator:** 52; 12.0 (0.4); White 39, African American 42, Other 19; 33.2 (0.7); 100 normal glucose tolerance and elevated hsCRP and/or fibrinogen concentrations >2 SDs
NCT00001723[64] USA, Y	**Orlistat:** 120 mg 3 times daily for 6 months **Placebo:** 120 mg 3 times daily for 6 months **Behavioural weight loss program:** 12-week intensive program	**Orlistat:** 65; 14.7 (1.4); non-Hispanic Black 63, non-Hispanic White 37; 41.7 (0.6); 100 systolic or diastolic hypertension, T2DM, IGT, hyperinsulinemia, hyperlipidaemia, hepatic steatosis or sleep apnoea **Placebo:** 66; 14.5 (1.5); Non-Hispanic Black 60, non-Hispanic White 40; 41.7 (0.6); 100 systolic or diastolic hypertension, T2DM, IGT, hyperinsulinemia, hyperlipidaemia, hepatic steatosis or sleep apnoea
NCT02273804[30] France, N	**Topiramate:** oral, according to theoretical weight (taken orally), escalated every 15 days. Patients who do not tolerate dose escalation reduced to the highest tolerated dose, 9 months. **Placebo**: oral, same dose regimen according to theoretical weight	**Topiramate:** 57.1; 12.4 [9.6–13.7]; NR; 32.6 [27.5–43.2]; NR **Placebo**: 40.0; 15.0 [11.8–16.8]; NR; 36.5 [31.7–49.3]; NR
NCT03338296[31] USA, Y	**Lorcaserin hydrochloride XR:** oral, 20 mg once daily, 52 weeks **Placebo**: oral, once daily	**Lorcaserin hydrochloride XR:** 59.6; 14.1 (1.59); not Hispanic or Latino: 67.6%; Hispanic or Latino: 32.4%; NR; NR **Placebo**: 61.2; 14.2 (1.58); not Hispanic or Latino: 57.9%, Hispanic or Latino: 42.4%; NR; NR
Ozkan[56] Turkey, N	**Orlistat:** oral, 3 doses per day, 120 mg × 3 (360 mg)/d, mean 11.7 months. Length of treatment was not consistent across participants **No placebo comparator**	**Orlistat:** 67; 12.9 (2.4); NR; 32.5 (no SD); NR **No placebo comparator:** 67; 12.5 (2.2); NR; 31.2 (no SD); NR

(Continues)

TABLE 1 (Continued)

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
	Lifestyle modification program: included reducing daily calories. Was administered by a team comprising of a paediatric endocrinologist, paediatrician and a dietitian. Participants seen by dietitian monthly and in the outpatient clinic every 2 months. Length = between 6 and 17 months	
Pastor-Villaescusa[35] Spain, N	**Metformin:** oral, initial dose 50 mg twice daily during meals for 10 days, and then 500 mg twice daily, 1 g/d, 6 months **Placebo:** twice daily during meals **Healthy lifestyle advice** at the beginning of a 1-on-1 session according to recommendations for food consumption frequency following the Mediterranean diet criteria and the physical activity. Length = 6 months	**Metformin:** 49; 6.8–15.3; White 100; prepubertal: 28.2 (SE 0.6), pubertal: 29.4 (SE 0.5); none **Placebo:** 49; 6.8–15.3; White 100; prepubertal: 29.2 (SE 0.6), pubertal: 30.6 (SE 0.5); none
Prado[57] Chile, N	**Metformin:** oral, once daily, 500 mg, 3 months **Placebo:** oral, once daily, 3 months **Nutritional guide and exercise program:** according to pattern 1500 kcal/d. Exercise classes once per week and exercise guide to be practiced twice per week. Length = 3 months	**Metformin:** 100; 15.6 (1.9); NR; 33.6 (no SD); 30.0 psychiatric comorbidities, at least one risk factor for T2DM (e.g., first- or second-degree relative with history of T2DM) **Placebo:** 100; 15.6 (1.9); NR; 33.3 (no SD); 11.1 psychiatric comorbidities, at least one risk factor for T2DM (e.g. first- or second-degree relative with history of T2DM)
Rezvanian[58] Iran, N	**Metformin:** oral, once daily, 1500 mg/d, 12 weeks (dosage increased weekly from 500 mg/d to 1500 mg/d) **Fluoxetine:** oral, once daily, 20 mg/d, 12 weeks (initial dosage 10 mg, increased to 20 mg/d after 3 weeks) **Metformin + fluoxetine:** oral, once daily, dosage not given, 12 weeks (single drug) **Placebo:** oral, once daily, 12 weeks **Healthy eating and physical activity advice:** physical activity advice included reducing sedentary time and taking part in 30 min of enjoyable, moderate-intensity physical activity per day. A registered dietitian conducted a nutrition education session with recommendations on diet such as increasing consumption of fruit and vegetables and not using hydrogenated fat	**Metformin:** NR; 13.1 (1.4); NR; 26.4 (0.5); NR **Fluoxetine:** NR; 13.5 (1.2); NR; 26.5 (0.7); NR **Metformin + fluoxetine:** NR; 13.7 (1.1); NR; 26.6 (0.8); NR **Placebo:** NR; 13.4 (1.4); NR; 26.2 (0.6); NR
Srinivasan[59] Australia, N	**Metformin:** oral, 2 doses per day, dose gradually built up to 1 g × 2 (2 g)/d, 6 months **Placebo:** oral, 2 doses per day, dose gradually built up to 1 g × 2 (2 g)/d, 6 months **Standardized information on healthy eating and exercise:** no further information given	**Both groups:** 54; 12.5 (2.2); 'ethnic backgrounds with high prevalence of insulin resistance and the metabolic syndrome (e.g., Indian subcontinent, Pacific islands) 64, northern European 25, mixed 11; NR; 89 acanthosis nigricans
van der Aa[34] The Netherlands, N	**Metformin:** immediate release, oral, 500 mg, increasing dose regimen with maximum dose of 2 tablets twice daily by week 4, 2 g/d, during or after breakfast and dinner, 18 months **Placebo:** oral, up to 2 g/d, during or after breakfast and dinner, 18 months **Physical training** by a physical therapist, twice weekly	**Metformin:** 73.9; median 13.6 (IQR 12.6–15.3); Caucasian 100; median 29.8 (IQR 28.1–34.5); T2DM 65.2, hypercholesterolemia 60.9, hypertension 69.5, CVD 60.9 **Placebo:** 57.9; median 12.0 (IQR 11.3–14.0); Caucasian 100; median 30.5 (IQR 28.7–38.6); T2DM 47.4, hypercholesterolaemia 47.4, hypertension 68.4, CVD 73.7
Van Mil[60] The Netherlands, Y	**Sibutramine:** oral, once daily, 5 mg/d, 12 weeks **Placebo:** oral, once daily, 5 mg/d, 12 weeks **Energy-restricted diet and exercise plan:** the energy prescription calculated from measured basal	**Sibutramine:** 45; 14.1 (1.0); NR; 30.1 (4.5); NR **Placebo:** 58; 13.8 (1.5); NR; 33.3 (5.0); NR

TABLE 1 (Continued)

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
	metabolic rate multiplied by an estimated physical activity level minus 500 kcal. Physical activity prescribed based on individual preferences and information obtained by physical activity questionnaire. It contained a daily bout of exercise of at least 30 min. Length = 12 weeks	
Warnakulasuriya[36] Sri Lanka, N	**Metformin:** 8–10 year: oral, 250 mg daily for a week and increased to 250 mg twice daily for a week and thereafter 500 mg twice daily; 11–16 years: 500 mg daily for 1 week and increased to 500 mg twice daily for a week and thereafter 1 g twice daily, with morning and evening meals, 12 months **Placebo:** oral, twice daily, 12 months **Diet and exercise:** age-based portion size guide, daily physical activity routine 20–30 min given to each child and weekly physical activity group sessions of 1 h, 12 months	**Metformin:** 28; 11.9 (2.2); NR; 27.4 (3.0); metabolic syndrome 22 **Placebo:** 38; 12.3 (2.3), NR; 27.4 (2.7); metabolic syndrome 12
Weghuber[40] Austria, Sweden, Y	**Exenatide:** subcutaneous injection, weekly, 2 mg/week, 24 weeks, administered by the patient following individual training or administered by trained adult or personnel at the study site. **Placebo:** subcutaneous injection once weekly, 24 weeks, administered by the patient following individual training or administered by trained adult or personnel at the study site. **Diet, exercise, psychological and behavioural:** nutritional intervention (four individual sessions), traffic light system, dividing foods and drinks into red (alert), orange (consider amount) and green (ok, when hungry or thirsty). Four individual psychological sessions were conducted aiming to optimize issues related to disturbed eating behaviour, sleep pattern, media consumption and sedentary behaviour in general, as well as to increase structured (at least one session per week in addition to physical education at school) and nonstructured physical activity, targeted the participants' 'health competence'	**Exenatide:** 59; 14.5 (2.3); White 100; 36.0 (4.8); none **Placebo:** 31; 13.5 (2.3); White 85, Asian 5, Black 5, other 5; 36.2 (5.0); none
Weghuber[43] Austria, Belgium, Croatia, Ireland, Mexico, Russian Federation, UK, USA; Y	**Semaglutide:** subcutaneous injection, weekly, dose escalation period 16 weeks, from 0.25 mg escalation every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg/maximum tolerated dose, 68 weeks **Placebo:** subcutaneous injection, weekly dose, 68 weeks **Lifestyle intervention:** 12-week lifestyle intervention run-in phase before randomization. Counselling about healthy nutrition and physical activity for weight loss from start of run-in to end of follow-up (87 weeks)	**Semaglutide:** 63; 15.5 (1.5); Asian 2, Black 8, White 78, other 12; 37.7 (6.7); 20.1 dyslipidemia, 13.4 hypertension, 3.7 T2DM, 1.5 obstructive sleep apnea **Placebo:** 61; 15.3 (1.6); Asian 1, Black 7, White 82, other 9; 35.7 (5.4); 14.9 dyslipidemia, 13.4 hypertension, 4.5 T2DM, 1.5 obstructive sleep apnea
Wiegand[61] Germany, Switzerland; Y	**Metformin:** oral, twice daily, 2 × 500 mg (1 g)/d, 6 months **Placebo:** oral, twice daily, 6 months **Behaviour-changing intervention:** an interview was performed before randomization to determine 1 to 3 individually chosen tasks (goals). Multi-professional reinforcement sessions took place every 4 to 8 weeks. Regarding physical activity, participants and their families attended specialized sport classes (2 sport classes per week, 45 min each, was recommended) in	**Metformin:** 72; 15.1 (no SD); White 87, Other 13; 34.3 (5.0) **Placebo:** 62; 15.0 (no SD); White 92, Other 9; 35.5 (5.8) Both groups: at risk of developing T2DM (obesity, acanthosis nigricans, signs of the metabolic syndrome, IFG and positive family history of T2DM or with IGT

(Continues)

TABLE 1 (Continued)

Trial, country, industry funding (Y/N/NR)	Intervention(s): drug component (route, frequency, total dose/d, duration) Comparator(s): drug component (route, frequency, total dose/d, duration) Co-intervention (s)	Participant characteristics: % female; mean age (yr, SD); % ethnic group; mean BMI (SD); n/% comorbidities
	addition to regular sport classes at school. Length = 6 months	
Wilson[62] USA, N	**Metformin:** oral, 4 times daily, 4 × 500 mg (2 g)/d, 48 weeks **Placebo:** oral, 4 times daily, 48 weeks **Behaviour-changing intervention**: used the Weigh of Life LITE program developed at Texas Children's Hospital, Houston. There were 10 individualized 'intensive' sessions at weekly intervals and monthly follow-up sessions for the reminder of the trial. Sessions led by trained health specialist and parent/guardians were invited. Length = 48 weeks	**Metformin:** 67; 14.8 (1.3); White 56, African American 21, Asian 8, Other 15, Hispanic 18; 35.9 (5.7); NR **Placebo**: 66; 15.0 (1.5); White 71, African American 16, Asian 0, Other 13, Hispanic 29; 35.9 (4.7); NR
Yanovski[63] USA, Y	**Metformin**: oral, twice daily, 2 × 1000 mg (2000 mg)/d, 6 months **Placebo**: oral, twice daily, 6 months **Dietitian-administered weight reduction program**: each participant and parent/guardian met with a dietitian monthly, who promoted a reduced-energy diet, increased physical activity and decreased inactivity. Participants trained to complete a 7-day food diary, which was used to prescribe a 'traffic light' style 500 kcal/d deficit diet, and exercise was encouraged for 30 min/d, monitored by pedometers readings. Length = 6 months	**Metformin**: 57; 10.1 (1.6); non-Hispanic White 42, non-Hispanic Black 42, Hispanic White 11, other 5; 34.2 (6.8); 26.4 paediatric metabolic syndrome, 64 acanthosis nigricans, 100 fasting hyperinsulinemia **Placebo**: 64; 10.4 (1.4); non-Hispanic White 49, non-Hispanic Black 38, Hispanic White 11, other 2; 34.6 (6.2); 31.9 paediatric metabolic syndrome, 68 acanthosis nigricans, 100 fasting hyperinsulinemia

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; HsCRP, high sensitivity C-reactive protein; HOMA, Homeostatic Model Assessment for Insulin Resistance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; IQR, inter-quartile range; kcal, kilocalories; LDL, low-density lipoprotein; min, minute; MRI, magnetic resonance imaging; N, no; NR, not reported; SD, standard deviation; SE, standard error; T2DM, type 2 diabetes mellitus; Y, yes; YMCA, Young Men's Christian Association; yr, year;/d, per day.

trials[39,40,43,47,61] were conducted in multiple countries. The length of intervention ranged from 12 weeks[57,58,60] to 2 years.[32] Five RCTs[39,43,58,60,62] reported data after a follow-up period of no treatment. The number of participants within each trial in these meta-analyses ranged from 20[60] to 533.[47] Mean ages within trials ranged from 8.8[37] to 16.3 years[52] with only three trials[37,44,63] with a mean age of <12 years. One trial[35] did not report mean age but included a range of 6.8–15.3 years. Proportion female ranged from 28%[36] to 100%.[57] Most participants were White; the proportions of other race and ethnicity ranged from 0%[37] to 63%.[64] Mean BMI ranged from 26.2[58] to 41.7 kg/m^2.[54] Nineteen trials reported comorbidities or risk factors for comorbidities in participants, at baseline. Drug agent included metformin ($n = 17$), sibutramine ($n = 6$), orlistat ($n = 4$), topiramate ($n = 2$), lorcaserin (1), phentermine+topiramate ($n = 1$), exenatide ($n = 2$), liraglutide ($n = 1$) and semaglutide ($n = 1$). Most trials included a concomitant behaviour-changing intervention and placebo as comparator. Four trials[38,48,55,56] did not report a placebo comparator, and another four trials[30,31,37,50] did not report any concomitant behaviour-changing intervention. Concomitant behaviour-changing interventions were heterogeneous in terms of content (diet and/or physical activity advice and/or behavioural therapy), without any standardization of intensity, delivery method, family involvement, setting or provider.

3.1 | Outcomes

Table 2 summarizes the certainty of evidence ratings for the seven outcomes. Meta-analysis results all relate to continued medication up to that point.

3.2 | BMI

Moderate certainty evidence from 25 trials ($N = 3088$) with follow-up of 6 months to 2 years (on medication) showed a significant reduction in BMI for intervention versus comparator (−1.71 kg/m^2 [95% CI: −2.27 to −1.14], $I^2 = 85\%$). Ten trials were excluded from BMI analysis, of which five[49,56–59] were excluded from the BMI analysis in the Cochrane review due to methodological concerns,[12] two were terminated trials,[30,31] one[37] reported insufficient data, and two were classed as weight loss maintenance trials and data were reported separately.[33,41] Drug type explained approximately 44.46% of heterogeneity. Bayes factors demonstrated strong evidence for the presence of an effect (BF10 >100) and heterogeneity (BF10 >100). There was no overall evidence of publication bias (BF = 0.25). Results of individual bias methods supported this. The average statistical power across

TABLE 2 Summary of findings.

Drug interventions compared with placebo/no placebo comparator for children and adolescents living with obesity					
Population: children and adolescents living with obesity (mean age 9.6 to 16.3 years) Settings: any (mainly outpatient settings) Intervention: any anti-obesity intervention usually combined with behaviour-changing interventions Comparison: placebo or no placebo usually with any behaviour-changing interventions Concomitant therapies were required to be the same in both the intervention and comparator groups. Minimum of 3 months' pharmacological intervention and 6 months' follow-up from baseline.					
	Illustrative comparative risks* (95% CI)				
	Assumed risk	**Corresponding risk**			
Outcomes	**Comparator**	**Drug intervention**	**Relative effect (95% CI)**	**Number of participants (trials)**	**Certainty of the evidence (GRADE)**
BMI (kg/m^2) Follow-up: 6 months–2 years	The mean reduction in BMI ranged across control groups from −1.8 to +1.2	MD **1.71 lower** (2.27 to 1.14 lower)	-	3088 (25)	⨁⨁⨁⊖[a] **Moderate**
BMI as percentage of 95th percentile Follow-up: 24–68 weeks	The mean BMI percentage points 95th percentile ranged across control groups from −4.2 to +4.97	MD **11.88 lower** (18.44 to 5.32 lower)	-	668 (5)	⨁⨁⊖⊖[b] **Low**
Serious adverse events Follow-up: 6 months–2 years	Absolute risk is 26 per 1000	Absolute risk is 35 per 1000 Absolute risk increase is ∼9 per 1000	**RR 1.22** (0.70 to 2.10)	1969 (8)	⨁⨁⨁⊖[c] **Moderate**
Health-related quality of life (IWQoL-kids questionnaire) Follow-up: 6–18 months	The mean health-related quality of life ranged across control groups from +82.4 to +87.1**	MD **1.95 higher** (0.06 to 3.85 higher)	-	717 (4)	⨁⨁⨁⊖[d] **Moderate**
Type 2 diabetes	Not reported				
Social functioning	243 participants (2 trials) included in 'health-related quality of life' outcome (see above), report subscales 'physical comfort; body esteem; social life; family relations'.				
Self-esteem	243 participants (2 trials) included in 'health-related quality of life' outcome (see above), report subscales 'physical comfort; body esteem; social life; family relations'.				

Note: GRADE Working Group grades of evidence: High certainty: Further research is very unlikely to change our confidence in the estimate of effect. Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low certainty: We are very uncertain about the estimate.

Abbreviations: BMI, Body mass index; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IWQoL-kids, Impact of Weight on Quality of Life-Kids; MD, mean difference.

[a]Downgraded once for inconsistency due to high heterogeneity ($I^2 = 84\%$, $p < 0.001$). Drug type accounted for approximately 46% of the heterogeneity and was a significant moderator.

[b]Downgraded twice, once for inconsistency due to high heterogeneity ($I^2 = 95\%$, $p < 0.001$) and once for imprecision (moderate number of studies).

[c]Downgraded once for imprecision (low number of events and the confidence intervals for the effect on serious adverse events are consistent with both an appreciable benefit and appreciable harm.

[d]Downgraded once for imprecision (small number of studies).

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio.

**Only 2 trials reported overall score for IWQoL-Kids.

studies to detect the pooled effect was 75%. Figure 1 shows the meta-analysis of BMI.

Reduction in BMI varied according to drug: exenatide −1.0 kg/m^2 (95% CI: −4.22 to 2.22, $N = 44$), liraglutide −1.58 kg/m^2 (95% CI: −2.47 to −0.69, $N = 251$), metformin −1.27 kg/m^2 (95% CI: −1.69 to −0.85, $N = 1024$), orlistat −0.79 kg/m^2 (95% CI: −1.08 to −0.51, $N = 773$), phentermine/topiramate −4.57 kg/m^2 (95% CI: −6.16 to −2.98, $N = 223$), semaglutide −5.88 kg/m^2 (95% CI: −6.99 to −4.77, $N = 201$) and sibutramine −1.70 kg/m^2 (95% CI: −2.92 to −0.48, $N = 568$).

There was no evidence of moderation by the length of treatment (X^2 (1) = 2.47, $p = 0.116$), age of the sample (X^2 (1) = 0.05,

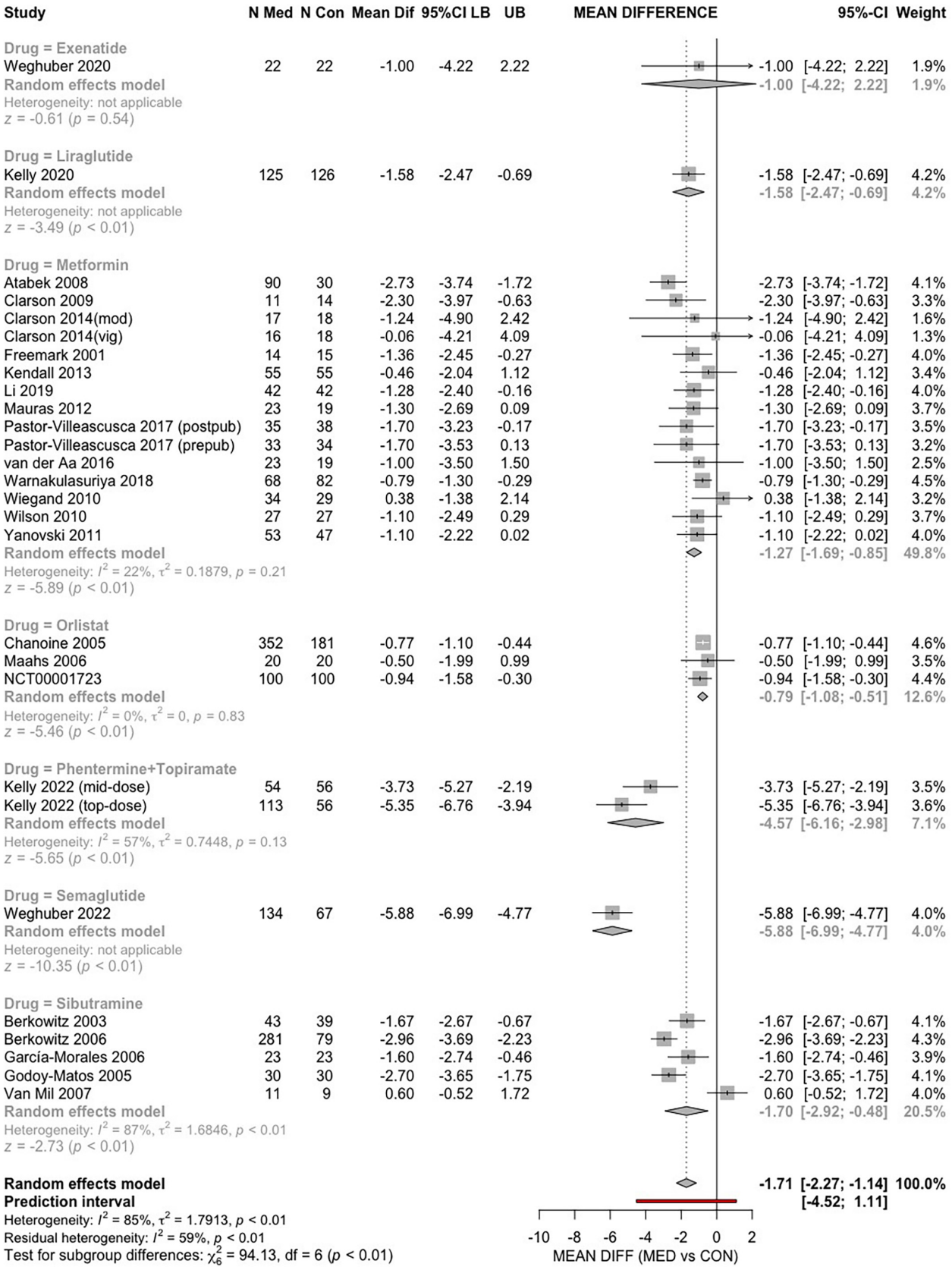

FIGURE 1 Meta-analysis of body mass index and anti-obesity medication + behaviour-change vs. behaviour change. The size of the squares is proportional to the weight of each study. Horizontal lines indicate the 95th confidence interval of each study, diamond indicates the pooled estimate with 95% confidence interval, N is the number of participants at baseline, and RR is relative risk.

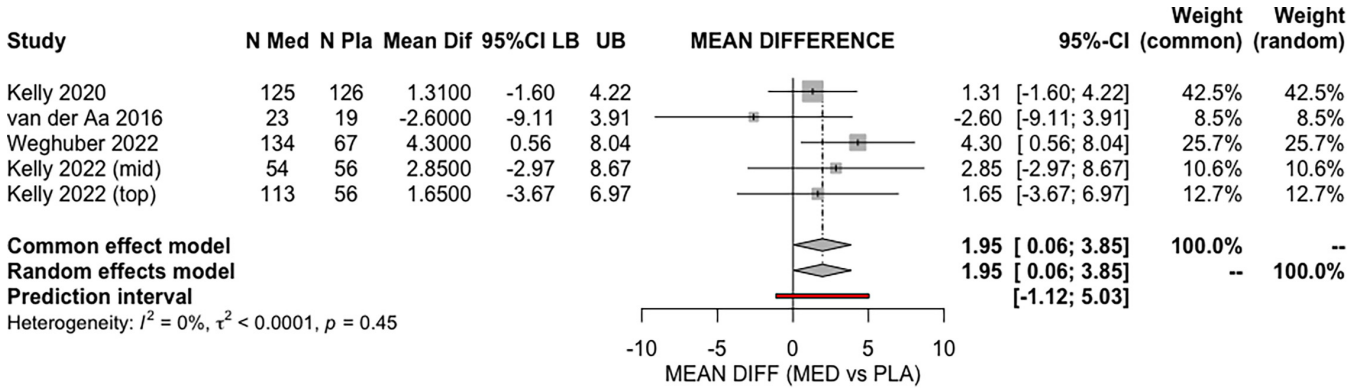

FIGURE 2 Meta-analysis of quality of life, anti-obesity medication + behaviour-change vs. behaviour change. The size of the squares is proportional to the weight of each study. Horizontal lines indicate the 95th confidence interval of each study, diamond indicates the pooled estimate with 95% confidence interval, N is the number of participants at baseline, and RR is relative risk.

$p = 0.831$) and original review studies versus studies from update search (X^2 (1) = 3.39, $p = 0.070$). Pooled data from seven comparisons of drugs that are approved by at least one agency showed reduction in BMI of −2.64 kg/m^2 (95% CI: −4.32 to −0.96, $N = 1448$). Pooled data from 26 comparisons of drugs that are approved or are used off-label showed reduction in BMI of −1.71 kg/m^2 (95% CI: −2.36 to −1.05, $N = 2520$).

Two trials reported on pharmacotherapy for weight maintenance following weight loss (behaviour change for all arms). Four weeks of meal replacement (participants encouraged to reach at least 5% BMI reduction) followed by 24 weeks of 75 mg/day topiramate resulted in mean difference BMI of −0.81 kg/m^2 (95% CI: −2.15 to 0.53) compared with meal replacement therapy alone, in 30 adolescents (mean age 15.2 years, mean BMI 40.3 kg/m^2).[33] Up to 8 weeks of meal replacement to achieve at least 5% BMI reduction ($n = 66/100$ achieved this and were randomized) followed by 52 weeks exenatide (2 mg weekly injection) resulted in mean difference BMI of −4.8 kg/m^2 (95% CI: −10.6 to 0.9) compared with placebo, in 66 adolescents (mean age 16 years, mean BMI 36.9 kg/m^2).[41]

3.3 | BMI as percentage of 95th Percentile

Low certainty evidence from six comparisons (five trials) ($N = 668$) with follow-up of 24–68 weeks shows a significant reduction in percent of the 95th percentile for BMI for intervention versus comparator (−11.88 percentage points [95% CI: −18.44 to −5.32], $I^2 = 96\%$). The average statistical power to detect this effect was 99% (eFigure 2 in Supplement).

3.4 | Adverse effects

3.4.1 | Serious adverse events

Moderate certainty evidence from eight comparisons (eight trials) ($N = 1969$) with follow-up from 6 months to 2 years shows no increased risk of serious adverse event for intervention versus comparator (3.5% vs. 2.6%; RR = 1.22 [95% CI: 0.70–2.10], $I^2 = 0\%$) (e-Figure 3 in Supplement). When only considering drugs that are approved (RR = 1.06 [95% CI: 0.59–1.89]) or approved combined with drugs used off-label (RR = 1.12 [95% CI: 0.63–1.98]), there was no increased risk for any adverse event.

3.4.2 | Dosage adjustment due to adverse events

There was an increased risk for an adverse event that led to drug dose adjustment, for intervention versus comparator (10.6% vs 1.7%; RR = 3.74 [95% CI: 1.51–9.26], $I^2 = 15\%$) (eFigure 4 in Supplement). When only considering drugs that are approved (RR = 8.41 [95% CI: 2.80–25.23]) or approved combined with drugs used off-label (RR = 3.74 [95% CI: 1.51–9.27]), the increased risk remained.

3.4.3 | Discontinuation of the trial due to adverse events

There was no increased risk for an adverse event that led to withdrawal from the study, for intervention versus comparator (4.6% vs 2.1%; RR = 1.51 [95% CI: 0.92–2.46], $I^2 = 0\%$) (eFigure 5 in Supplement). When only considering drugs that are approved (RR = 1.68 [95% 0.81–3.46]) or approved combined with drugs used off-label (RR = 1.83 [95% CI: 0.97–3.46]), the risk was not changed.

3.5 | Health-Related Quality of Life

Moderate certainty evidence from four trials ($N = 717$) with follow-up from 6 to 18 months shows an improvement in quality of life for intervention versus comparator (1.95 [95% CI: 0.06–3.85], $I^2 = 0\%$) using the Impact of Weight on Quality-of-Life scale-kids (IWQoL-kids). The average statistical power to detect this effect was 18%. Figure 2 shows meta-analysis of HRQoL. Supplemental analyses

including one study that used the SF36 scale demonstrated no significant difference between intervention vs comparator.

There were no data reported on T2DM, social functioning or self-esteem. There were very limited data reporting outcomes after a period of no-intervention follow-up.

4 | DISCUSSION

Overall, there was moderate certainty evidence that anti-obesity medication plus behaviour-changing intervention reduced BMI by 1.71 kg/m^2 for up to 2 years, compared to behaviour-changing intervention with or without placebo, in adolescents. When limited to currently approved drugs, BMI was reduced by 2.66 kg/m^2. This was accompanied by improvement in HRQoL and approximately 1 in 100 adolescents experiencing a serious adverse event. Low certainty evidence showed a reduction in percent of the 95th percentile for BMI of 11.88 percentage points. Evidence outside of this review for clinically important weight change is largely derived from zBMI (standardized measure of BMI used in children and younger adolescents). An Evidence Update for the US Preventive Services Task Force (USPSTF)[65] refers to evidence from a meta-regression,[66] which suggested that zBMI reductions of at least 0.7 are needed to show cardiometabolic improvement. Evidence from a systematic review[67] has shown that a 1-mm Hg decrease in systolic blood pressure was associated with a decrease of 0.16 kg/m^2 in BMI (42 interventions enrolling 3807 children mean age 12.2 years, mean BMI 31.7 kg/m^2). Therefore, a BMI reduction of 1.71 kg/m^2 in the current review appears consistent and indicates associated health benefits and compares favourably compared to behavioural interventions alone. The Evidence Update for the USPSTF[65] highlights mean reductions in zBMI found in behavioural intervention trials ranged from 0.2 to 0.4 depending on intensity of contact. The USPSTF Evidence Update[65] also reported that serious adverse events were rare for all anti-obesity medications and did not differ between groups, which concurs with findings from the current review.

Missing data for T2DM and psychosocial health highlight important evidence gaps. Evidence for younger children is limited. There is limited evidence for the role of anti-obesity medications for maintenance of weight loss following meal replacements. Very few studies reported outcomes after a period of no-intervention follow-up and so it remains unclear whether improvements in BMI are sustained longer term after anti-obesity medications are stopped. The Cochrane review[12] reported that three included trials showed that drug withdrawal was followed by weight regain.[58,60,62] This update included two trials[39,43] that reported a period of no-drug follow-up, and both reported some weight regain. Evidence in adults, from continued treatment with tirzepatide for maintenance of weight reduction (SURMOUNT-4),[68] showed that withdrawal led to substantial weight regain. Three hundred participants (89.5%) receiving tirzepatide at 88 weeks maintained at least 80% of the weight loss achieved during the 36-week lead-in period compared with 16.6% receiving placebo. Further research with adolescents is needed to see if initial weight loss, and associated health benefits, can be maintained when medication is stopped.

Drug type explained approximately 44% of heterogeneity in BMI (mean difference); however, care should be taken when comparing between individual groups due to small subgroup sizes.[69] The high drug-related heterogeneity gives us an average result that is not directly applicable to one specific drug. Moreover, subgrouping by drug agent helps clinicians to choose a drug. The largest reduction in BMI of 5.88 kg/m^2 (observed for semaglutide) was associated with beneficial changes in BMI category: 45% of adolescents taking 2.40 mg once-weekly subcutaneous semaglutide transitioned to the normal weight or overweight category (i.e., dropped below the obesity cut-off point by BMI) by 68 weeks compared to 12% of adolescents receiving placebo. All adolescents received a behaviour-changing intervention, which comprised of counselling in healthy nutrition and a goal of 60 min of moderate to vigorous physical activity per day.[70]

Further exploration of heterogeneity is required, both in terms of treatment effect and participant characteristics.[71] However, pharmacotherapy may present less heterogeneity compared to other treatment modalities. Secondary analysis of pooled data showed a high degree of heterogeneity in BMI reduction for adolescents with severe obesity across different treatment modalities, with pharmacotherapy showing less variation compared (indirectly) to behaviour-changing interventions or metabolic/bariatric surgery.[72] Further work is needed to understand the intensity of concomitant behaviour-changing interventions. For example, recent clinical practice guidelines of the American Academy of Pediatrics (AAP) state that metformin trials that reported greater effects in BMI reduction used a more intensive behaviour-changing intervention, administered higher doses of metformin or enrolled children and adolescents with more severe obesity.[11] The USPSTF Recommendation Statement 2017[73] recommends behavioural interventions with 26 or more contact hours for weight loss. Detailed reporting of the behaviour change components of future pharmacotherapy trials would enable comparison with these USPSTF recommendations.

The review findings support previous systematic reviews and meta-analyses.[74–82] The review is unique in that it covers the following critical features: it is the most comprehensive review because it includes all drugs used to treat children and adolescents living with obesity (regardless of regulatory approval), includes psychosocial outcomes that are prioritized by these young people and their parents,[17–19,22] focuses on longer term studies (6 months from baseline), which reflect a move towards treating obesity as a chronic and relapsing disease, and examines multiple sources of heterogeneity. Importantly, none of the previously published systematic reviews or latest treatment guidelines include RCT evidence from phentermine/topiramate and semaglutide, which have now been approved by the U.S. Food and Drug Administration (FDA).[74–82]

The overall effects of the meta-analyses integrate drugs that vary in their mechanism of action. Due to the rapid development of new agents and their application to paediatric age, drugs from the 'first generation' (e.g., metformin and orlistat) may no longer be the first choice for prescribing. Sibutramine was approved by the FDA in 1997

but then withdrawn in 2010 due to its cardiovascular risk increase. From 2010 until 2020, orlistat was the only approved drug for treating children aged 12 and older living with obesity.[83] Four drugs are now approved starting at age 12: orlistat, liraglutide, phentermine/topiramate and semaglutide. In 2021, both the FDA and the European Medicines Agency (EMA) approved liraglutide for the treatment of obesity in children and adolescents aged ≥12 years.[84,85] In addition, the FDA approved phentermine/topiramate in 2022, which was also re-evaluated by the EMA without approval due to the high chance of side effects.[86,87] Recently, both the FDA and the EMA have approved semaglutide for the treatment of paediatric obesity from 12 years onwards.[88,89] Other drugs are only used 'off-label', for example, metformin and exenatide.[90] Post hoc analyses show that the overall effect size for BMI reduction (all drugs) is conservative when compared to only drugs that are currently approved, with a difference of approximately 1 kg/m^2 in favour of the four currently approved drugs. However, data suggest that adverse event leading to discontinuation of the study is an increased risk for all anti-obesity medications regardless of approval status. Due to their higher efficacy, semaglutide and phentermine/topiramate might be classified as anti-obesity drugs from the 'new era' (eFigure 6 in Supplement).

A clear strength of this review is that it contains all current and ongoing evidence ready for the next update, including 10 ongoing RCTs, which will add to the future evidence base. In addition, RCTs of new drug agents are currently underway in adults living with obesity, which might be investigated in paediatric populations if proven to be safe and effective in adult populations.[91] However, of the 10 ongoing trials in the paediatric population, it appears that only two will report on 95th percentile BMI and only one will report on HRQoL.[92–94]

It is important to note that guidelines recommend pharmacotherapy for adolescents living with obesity, only as an adjunct to multicomponent behaviour-changing treatment.[11,95] The updated AAP Clinical Practice Guideline for treating childhood obesity considers (for the first time) the use of pharmacotherapy for children and adolescents who require an additional treatment option to manage their obesity. This refers specifically to older children, children living with BMI ≥95th percentile and children with severe comorbidities.[11] A recent commentary published in the Lancet highlights the challenges relating to equitable and safe use of these newer medications for the health of adolescents living with obesity, including the need for adequate training of physicians and healthcare professionals, unknown long-term effects and the need to deliver pharmacological treatment as an adjunct treatment within a person-centred and lifelong care approach.[96] We identified two trials[97,98] of bariatric surgery, which were excluded because the duration was less than 6 months. However, there continues to be advances in obesity management across all treatment modalities, including combinations and direct comparisons of pharmacotherapy, bariatric surgery and behavioural components (e.g., meal replacements versus GLP-1 RA and stepped approaches using anti-obesity medications according to behavioural treatment response).

It is well known that the incidence and prevalence of obesity in childhood and adolescence is unequal, represented by a higher risk for obesity in socioeconomically disadvantaged children and adolescents.[99–101] Furthermore, there are social disparities in obesity management even though the evidence base is weak.[102] It is therefore imperative that drug intervention is only considered as part of a suite of options addressing obesity as a complex and chronic disease with effective comorbidity management and careful adverse event monitoring that is underpinned by a person-centred care approach, delivering healthcare with dignity and respect.[11,103,104]

4.1 | Limitations

This review has several limitations: Firstly, limitations relating to the representativeness of the participants. Only three trials included children with a mean age younger than 12 and one other trial reported outcomes by pubertal status, which limits wider applicability of findings. This is coupled with limited racial and ethnic diversity within the trials and a paucity of data from low- and middle-income countries.

Secondly, considerations related to the uncertainty of the data. Meta-analyses of BMI and 95th percentile BMI showed high heterogeneity. For BMI, heterogeneity was partly explained by subgroup analysis on medication type. For 95th percentile BMI, there was insufficient evidence from the same drug type to examine heterogeneity and more studies reporting on this outcome are required. There were very few serious adverse events, hence the very wide confidence intervals. In addition, individual studies used different definitions of serious adverse events. Despite recommendations of the Cochrane review,[12] there remain little data on the longer term (post 2-year) sustainability of weight loss. This is crucial given recognition of obesity as a chronic and relapsing disease. Although data were limited for 95th percentile BMI (graded 'low certainty', downgraded for high heterogeneity and imprecision), this metric is increasingly used in obesity trials and will be important for future updates of this and other reviews because it is clinically important to use a range of metrics and percentage of the 95th percentile BMI may be more strongly associated with change in adiposity in children aged 3–7 years and in adolescents with severe obesity, when compared to BMI.[21,105,106]

Thirdly, issues relating to outcomes. We did not include outcomes that might be relevant for the prevention of comorbidities and consequential diseases, for example, the effects on insulin resistance or biomarkers. None of the included trials reported data on T2DM or psychosocial health explicitly, and while our data showed a trend for improvement in HRQoL using change in IWQoL-kids scores, sensitivity analyses including one study using the SF36 found no significant change overall. Effects on HRQoL were mainly driven by improvements in the physical comfort score domain, which is similar to findings in a recent review by Lister et al.,[107] which highlighted that improvements in HRQoL can occur in domains most affected by living with obesity, including physical functioning despite a lack of strong correlation between weight change and HRQoL. Ongoing trials should report on these outcomes, particularly considering the importance of psychosocial outcomes to young people, their parents and wider community.[17–19]

5 | CONCLUSIONS

In adolescents living with obesity, pharmacotherapy in addition to behaviour change was associated with significantly reduced BMI, which varied according to drug and with 1 in 100 adolescents experiencing a serious adverse event. It remains unknown whether anti-obesity mediations improve the psychosocial health of children and adolescents living with obesity.

AUTHOR CONTRIBUTIONS

Dr Brown had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Torbahn, Ells, Gartlehner, Kelly, Weghuber and Brown helped in concept and design. All authors contributed to acquisition, analysis and interpretation of data. Torbahn and Brown drafted the manuscript. All authors critically revised the manuscript for important intellectual content. Jones helped in statistical analysis. Metzendorf contributed to administrative, technical and material support. Brown supervised the study.

FUNDING INFORMATION

This project was largely unfunded; Cochrane Austria supported the study with internal funds, which funded Metzendorf to conduct the searches and Jones to conduct the statistical analyses.

This project was largely unfunded, except for the searches and the statistical analyses. Cochrane Austria had no role in the conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript findings. The opinions expressed in this document are those of the authors.

CONFLICT OF INTEREST STATEMENT

Dr Brown received funding from the Office of Health Improvement and Disparities and received funding from the National Institute for Health Research. Prof. Ells received funding from the National Institute for Health Research, Medical Research Council, Office of Health Improvement and Disparities. She also teaches on the EASO summer school and is an author on the ACTIONTeens project but does not receive any financial reimbursement for these roles. Prof. Kelly engages in unpaid consulting activities for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Vivus and received donated drug/placebo from Novo Nordisk and Vivus for US National Institutes of Health-funded clinical trials. Prof. Weghuber received advisory board fees and honorarium as a speaker from Novo Nordisk. No other disclosures were reported.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Torbahn G, Jones A, Griffiths A, et al. Pharmacological interventions for the management of children and adolescents living with obesity—An update of a Cochrane systematic review with meta-analyses. *Pediatric Obesity*. 2024;19(5):e13113. doi:10.1111/ijpo.13113