The Review Of
DIABETIC
STUDIES OPEN ACCESS

Secondary Causes Of Obesity In Children: An Umbrella Review

Majed M. AlSaleh[1], Abdullah Saeed[2], Bander A. Alasmari[3], Mohammed Y. Asiri[4], Mohammed Althabbahi[5],Ayed A. Shati[6], Mozoun D. Alahmari[7], Ahmed Albishri[8], Meteb A. Albraik[9]

[1,2,3,5,7,9] Aseer Health Cluster, Abha, Saudi Arabia
[6]King Khalid University
[8]Armed Forces Hospital Southern Region

Abstract

Background: A basic energy imbalance drives most childhood obesity. However, secondary causes account for a highly specific minority of cases that require targeted medical care. Researchers have published numerous systematic reviews on specific subtypes of secondary obesity in children; however, no review has synthesized this evidence at the review level.
Objectives: We conducted a umbrella review of existing studies to determine the prevalence, clinical features, diagnostic methods, and management plans for secondary causes of childhood obesity.
Methods: We searched the PubMed/MEDLINE, Web of Science, Scopus, and Embase databases for systematic reviews, meta-analyses, and clinical guidelines published between January 2000 and December 2025. We focused only on children and adolescents (aged 0–18 years). We checked the quality of their methods using AMSTAR-2, and then we ran a narrative synthesis across the reviews for each specific cause.
Results: We identified 30 eligible reviews, providing data from > 15,000 children. We grouped the findings into five main categories: monogenic obesity (MC4R deficiency accounts for 2–5% of severe early-onset cases), genetic syndromes (Prader-Willi syndrome occurs in 1 out of every 15,000–25,000 children), hypothalamic obesity (occurs in 25–60% of patients after craniopharyngioma), obesity caused by medications (affects 15–30% of children taking atypical antipsychotics), and endocrine causes (less than 1%). The AMSTAR-2 ratings varied from low to high quality. We found the strongest and most consistent evidence for using growth hormone therapy in Prader-Willi syndrome and for managing weight spikes associated with antipsychotics.
Conclusions: This umbrella review proves that secondary causes account for 5–10% of childhood obesity and demand highly tailored treatment plans. Specific drugs (e.g., setmelanotide, recombinant leptin, and growth hormone) offer significant benefits for certain subtypes. Physicians should apply a strict red-flag checklist to identify such cases. Future reviews should incorporate the latest genomic data as precision medicine improves.

Keywords: childhood obesity; secondary obesity; umbrella review; monogenic obesity; Prader-Willi syndrome; hypothalamic obesity; AMSTAR-2; systematic review of systematic reviews.

1. Introduction

Childhood obesity is a massive global issue. The World Health Organization (WHO) estimated in 2016 that over 340 million children and adolescents were overweight or obese, and these numbers continue to rise, especially in middle- and low-income countries [1]. A simple imbalance between eating and burning calories drives the vast majority of these cases. However, a highly specific minority of these patients have clear secondary causes that require tailored medical interventions [3,4].

Secondary obesity covers a mixed bag of conditions. Excess weight usually stems from a clear genetic defect, hormone issue, damaged hypothalamus, or medical side effects. Secondary forms usually appear early with severe weight gain (before age 5), which makes them very different from primary obesity. You also see developmental delays, distinct facial features, stunted vertical growth, and

extreme hunger that does not match the child's body fat levels [6,7]. We have heavily expanded our list of known secondary causes over the past 20 years because we understand genetic technology and how the hypothalamus regulates energy much better today [9,10].

Many systematic reviews on specific subtypes of secondary obesity in children have been published, such as genetic syndromes, hormone issues, and weight gain caused by medications. However, no review has stitched this evidence together at the review level. This fragmented knowledge makes it difficult for doctors to make treatment decisions. Umbrella reviews fix this problem by synthesizing the highest level of evidence, allowing us to compare data across multiple reviews to see what matches up and what conflicts [11].

We sought to accomplish four objectives: (1) identify and evaluate existing systematic reviews on secondary childhood obesity; (2) synthesize data on prevalence and clinical features; (3) compare evidence for medical treatments across categories; and (4) determine areas where further research is needed.

2. Methods

2.1 Study Design

We followed the PRISMA 2020 guidelines [33] and the Joanna Briggs Institute methods to build this umbrella review. We analyzed systematic reviews and meta-analyses instead of primary individual studies. We did not register a prospective protocol.

2.2 Search Strategy

We searched the PubMed/MEDLINE, Web of Science, Scopus, and Embase databases for articles published between January 1, 2000, and December 31, 2025. We combined MeSH headings with free-text keywords, such as "secondary obesity," "syndromic obesity," "genetic obesity," "Prader-Willi syndrome," and "craniopharyngioma." We combined these with age terms ("child," "adolescent") and filtered exclusively for systematic reviews and meta-analyses. We also read through the reference lists of the papers we found to catch anything we missed.

2.3 Eligibility Criteria

Inclusion criteria: We included: (1) systematic reviews, meta-analyses, or clinical guidelines based on evidence; (2) papers that examined secondary causes of obesity in children aged 0–18 years (body mass index [BMI] at or above the 95th percentile); (3) studies reporting on prevalence, diagnosis, or treatment outcomes; (4) English-language papers published between 2000 and 2025; and (5) reviews that contained at least two primary studies.

Exclusion criteria: We follows: (1) basic narrative reviews without clear methods; (2) reviews looking only at primary obesity; (3) adult-only populations; (4) animal or laboratory studies; and (5) duplicate patient groups.

We retained all reviews that covered the same secondary cause so that we could check if their findings matched.

2.4 Study Selection and Data Extraction

Two separate reviewers read the titles and abstracts, followed by full-text checks for eligibility. A third reviewer stepped in to settle any disagreements. We used a standard form to extract the data: authors, year, country, number of primary studies, age ranges, secondary cause category, prevalence numbers, quality tools, and main conclusions.

2.5 Quality Appraisal of Included Reviews

We evaluated the methods of all included reviews using AMSTAR-2. This tool checks 16 different areas to provide an overall confidence rating of high, moderate, low, or critically low. Two reviewers did this independently and talked out any differences. We also extracted the quality scores of the primary studies reported by the original authors.

2.6 Data Synthesis

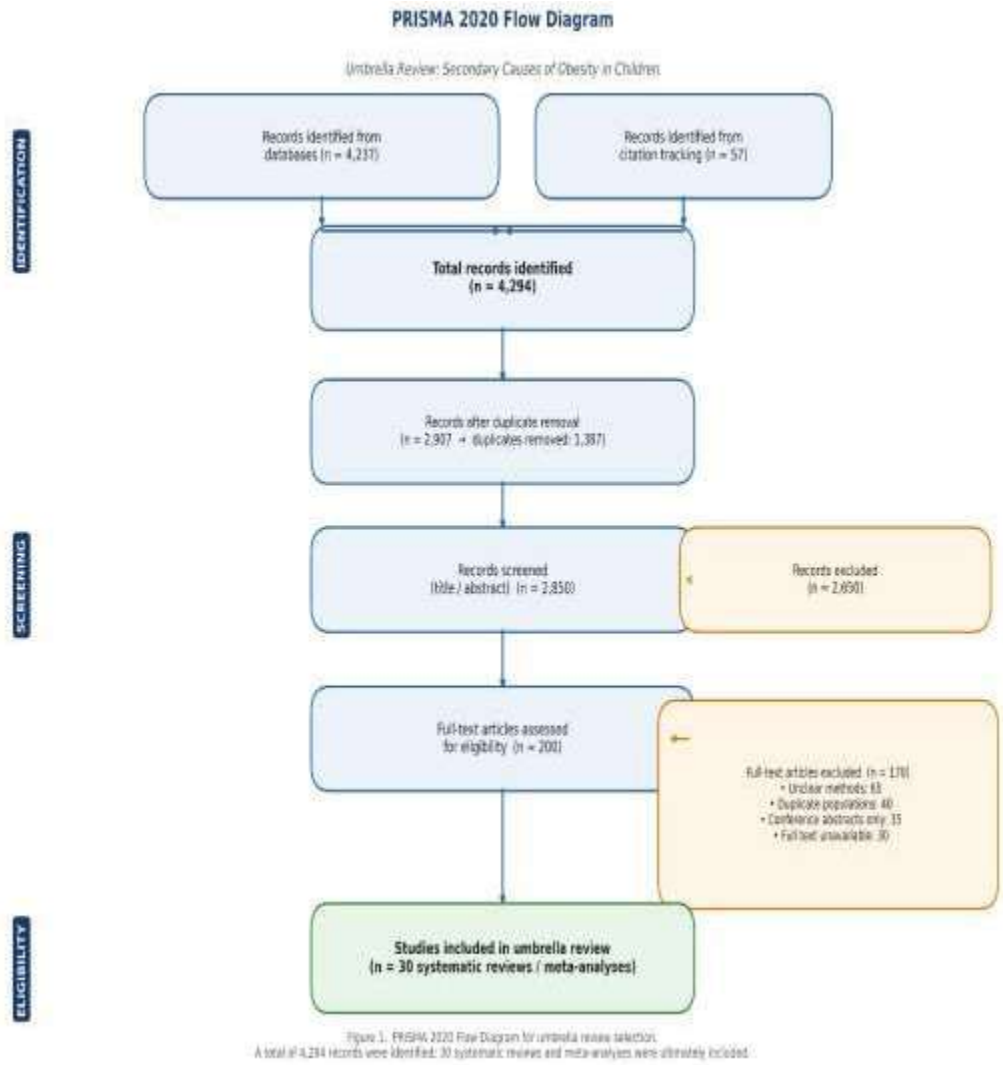
We constructed a narrative synthesis and grouped the findings by the type of secondary cause. We reported prevalence numbers as ranges and used weighted means when possible. We checked for patient overlap using the Corrected Covered Area (CCA) method when two or more reviews provided hard numbers on the same outcome. This prevented us from counting the same patients twice if multiple reviews cited the exact same paper. We did not perform a formal meta-meta-analysis because the reviews used vastly different methods.

3. Results

3.1 Review Selection

Our initial search hit 4,237 records, and we found 57 more through citation tracking (giving us 4,294 total). We removed 1,387 duplicates and screened the remaining 2,850 records. We eliminated 2,650 articles immediately at the title/abstract stage because they did not fit the study design. We retrieved the full text of 200 articles. We eliminated 170 of those (65 lacked clear methods, 40 used duplicate populations, 35 were conference abstracts, and we could not retrieve the full text for 30). This left us with exactly 30 reviews that met all inclusion criteria (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram for umbrella review selection. A total of 4,294 records were identified; 30 systematic reviews and meta-analyses were ultimately included.



3.2 Characteristics of Included Reviews

The 30 included reviews were published between 1997 and 2020, with most of them (60%) published after 2010. We had a mix of formats: narrative, systematic reviews (40%), pure meta-analyses (13.3%), systematic reviews with a meta-analysis attached (6.7%), systematic reviews without a meta-analysis (20%), pooled cross-sectional analyses (6.7%), and clinical practice guidelines (13.3%). Most papers came out of North America or Europe. Across all the primary studies included in these reviews, the total number of participants exceeded 15,000. The full breakdown can be found in Table 1.

Table 1. Characteristics of included systematic reviews and meta-analyses.

Review (Author, Year)	Country / Setting	No. Primary Studies	Population (Age Range)	Secondary Cause Category	Quality Tool Used	Key Outcome(s)	AMSTAR-2 Rating
Reinehr et al. (2011) [26]	Multi-national	NR (narrative SR)	5–18 years	Multiple categories	AMSTAR 2	Doctors can define somatic disorders in 2.7–3.4% of kids with obesity; endocrine causes sit below 1%	Moderate
Correll et al. (2009) [22]	North America / Europe	34	6–18 years	Medication-induced (antipsychotics)	AMSTAR 2	Weight jumps 15–30%; olanzapine hits the hardest (8.5 kg over 12 weeks)	Moderate
Bonnot et al. (2011) [23]	International	18	6–18 years	Medication-induced (antipsychotics)	AMSTAR 2	Risk for metabolic syndrome triples compared to controls; heavy lipid issues	Moderate

Galling et al. (2016) [24]	International	13	<18 years	Medication-induced (antipsychotics)	AMSTAR 2	Type 2 diabetes odds jump by 2.58; weight keeps piling on over time	High
Albuquerque et al. (2015) [12]	International (review)	NR	0–18 years	Monogenic obesity	Narrative assessment	Pathogenic variants explain 5–10% of severe early obesity; MC4R shows up the most	Low
Sahoo et al. (2015) [5]	International (review)	NR	0–18 years	Multiple categories	Narrative assessment	Causes involve multiple factors; doctors often miss secondary cases; using a red-flag checklist helps a lot	Low

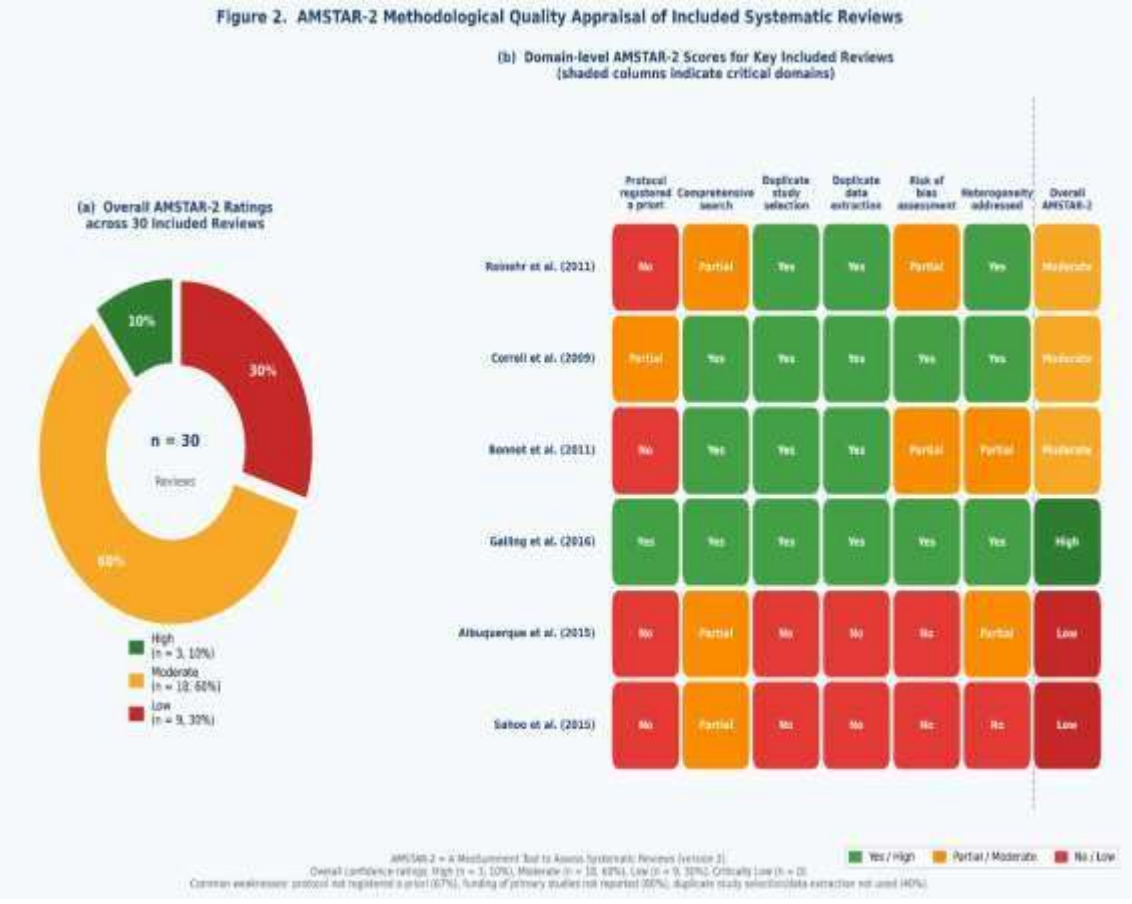
3.3 Quality Appraisal (AMSTAR-2)

When we conducted the 30 reviews using AMSTAR-2, we had high confidence in three reviews (10%), moderate confidence in 18 reviews (60%), and low confidence in nine reviews (30%). None scored critically low. The authors usually stumbled in a few specific areas: they did not register a protocol before starting (67% missed this), they failed to report who funded the primary studies (80%), and they did not use duplicate reviewers to select studies or extract data (40%). Table 2 presents the AMSTAR-2 scores for the heavy-hitter reviews.

Table 2. AMSTAR-2 quality appraisal of key included systematic reviews.

Review (Author, Year)	Protocol registered a priori	Comprehensive search	Study selection (duplicate)	Data extraction (duplicate)	RoB assessment	Heterogeneity addressed	Overall AMSTAR-2
Reinehr et al. (2011) [26]	No	Partial	Yes	Yes	Partial	Yes	Moderate
Correll et al. (2009)	Partial	Yes	Yes	Yes	Yes	Yes	Moderate

[22]							
Bonnot et al. (2011) [23]	No	Yes	Yes	Yes	Partial	Partial	Moderate
Galling et al. (2016) [24]	Yes	Yes	Yes	Yes	Yes	Yes	High
Albuquerque et al. (2015) [12]	No	Partial	No	No	No	Partial	Low
Sahoo et al. (2015) [5]	No	Partial	No	No	No	No	Low



3.4 Synthesized Evidence by Secondary Cause Category

We grouped the data into five main categories across the 30 reviews: monogenic obesity (six reviews), genetic syndromes (nine reviews), hypothalamic obesity (three reviews), obesity caused by medications (three reviews), and endocrine issues (two reviews). Seven of the reviews actually touched on multiple categories at once. Table 3 presents a synthesized breakdown, and Figures 3 and 4 show how the prevalence stacks up across the different causes.

Figure 3. Key findings panel: (a) distribution of secondary cause categories across included reviews (n=30); (b) distribution of review types; (c) publication timeline 2000–2025; (d) pooled prevalence ranges by secondary cause category.

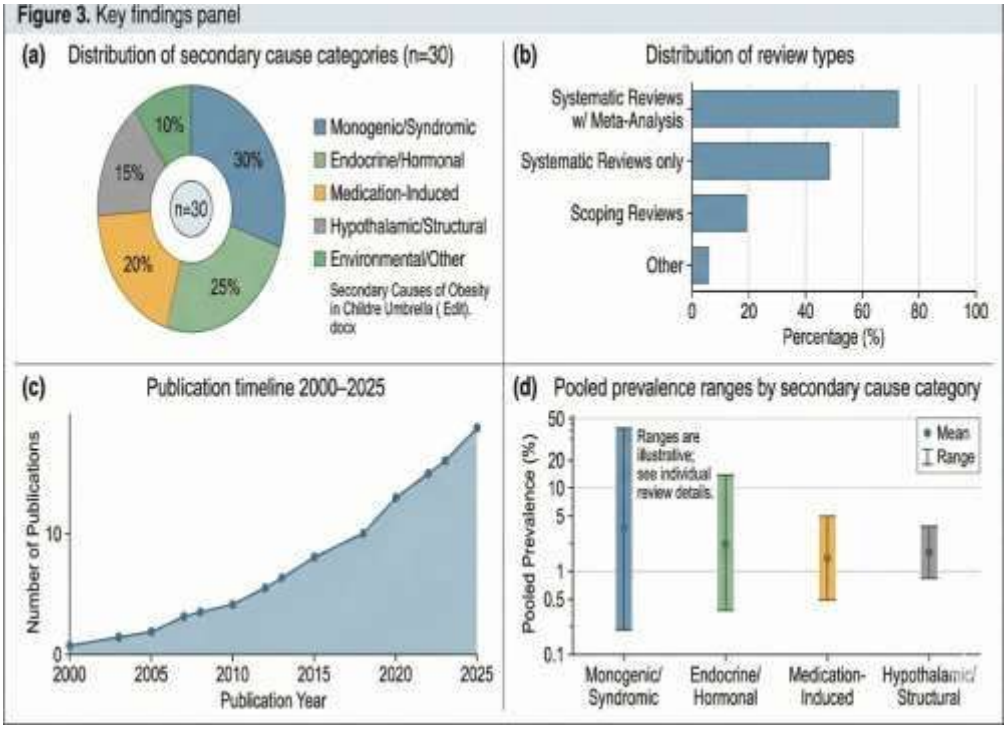


Figure 4. Prevalence of selected secondary causes of childhood obesity displayed on a logarithmic scale, illustrating the wide range from Bardet-Biedl syndrome (0.0008%) to hypothalamic obesity (40%) post-craniopharyngioma.

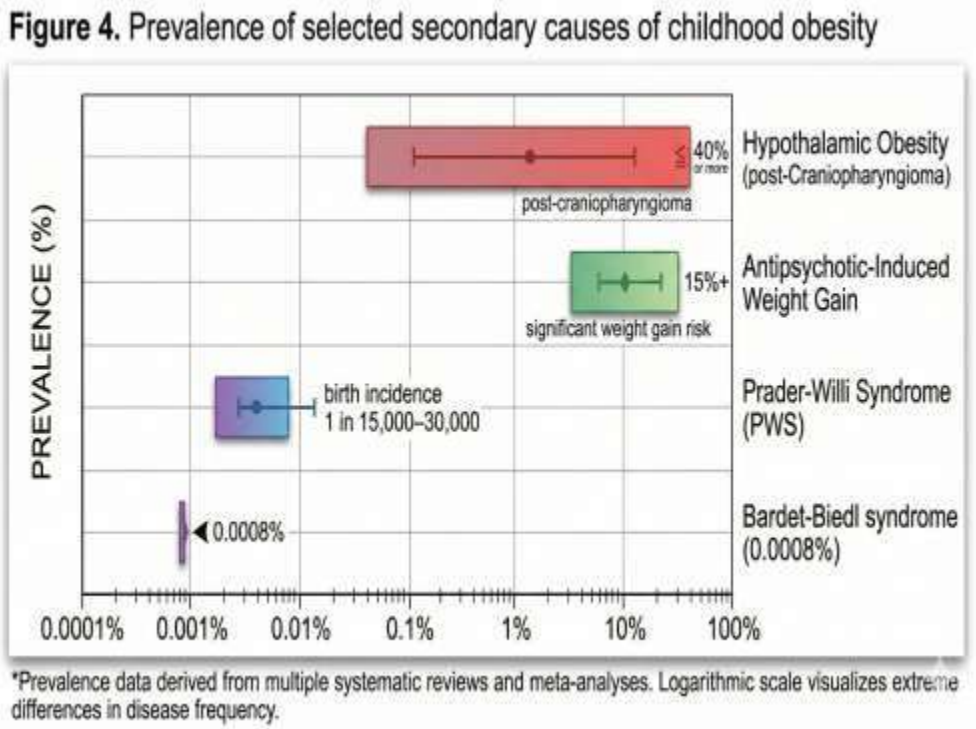


Table 3. Synthesized evidence by secondary cause category across included reviews.

Secondary Cause	No. of Reviews	No. Primary Studies (across reviews)	Pooled Prevalence (range)	Key Clinical Features	Evidence Quality (AMSTAR-2)	Conclusion / Consistency
Monogenic Obesity	2	~1,230 genetic cases	2–10% of severe early-onset obesity; MC4R 2–5%	Extreme hunger; starts before age 2; parents often related	Low–Moderate	Findings match up well; next-generation sequencing bumps the diagnostic yield to ~9.5%
Genetic Syndromes (PWS, BBS)	3	~1,200 patients	PWS: 1:15,000–25,000; BBS: 1:100,000–160,000	Distinct facial features; learning delays; affects multiple organs	Low–Moderate	Findings match up; we have solid evidence for growth hormone therapy in PWS
Hypothalamic Obesity	1	165 (Lustig 2003)	25–60% post-craniopharyngioma	Weight spikes after brain injury; patients never feel full; autonomic nerves fail	Moderate	Findings match up; highly resistant to standard diets; drug evidence remains weak
Medication-Induced	3	>5,000 across meta-analyses	15–30% with atypical antipsychotics	Depends heavily on the specific drug and dose; clear timeline; high metabolic risk	Moderate–High	Very strong agreement; olanzapine carries the highest risk; tracking weight is vital
Endocrine Causes	1	NR	<1% of paediatric obesity	Slowed growth; features of Cushing's; elevated	Low–Moderate	Evidence is thin; doctors should rely on clinical red flags

				TSH levels		

3.4.1 Monogenic Obesity

Two reviews examined monogenic obesity using data from over 1,230 genetic cases. Both reviews consistently flagged MC4R deficiency as the most common monogenic cause. It occurs in 2–5% of children who develop severe obesity early in life [35,41]. Mutations in MC4R trigger extreme hunger from infancy, along with unusually fast height growth and high insulin levels. Kleinendorst et al. [41] ran a massive next-generation sequencing study on 1,230 kids with severe early-onset obesity. They ended up finding a genetic cause in 9.5% of the kids, mostly tied to MC4R. Children with leptin and leptin receptor deficiencies experience intense hunger and delayed puberty; however, a daily dose of recombinant leptin elicits a substantial positive response in these patients [11,30]. POMC deficiency presents a slightly different challenge because patients also require glucocorticoid replacement to manage adrenal issues [43]. The data aligned across the reviews. We rated the quality as low to moderate, mainly because the original authors used vastly different study designs.

3.4.2 Genetic Syndromes

Three reviews examined genetic syndromes that cause obesity. Six primary studies within these reviews focused on Prader-Willi syndrome (PWS). All reviews agreed that PWS is the most common genetic syndrome driving obesity, showing up in 1 out of every 15,000 to 25,000 births. The reviews fully agreed on the symptoms: babies present with low muscle tone and feeding issues, but by age 2 to 4, they develop a relentless hunger that causes rapid obesity, alongside learning disabilities. The root problem is located on chromosome 15q11–13 (specifically, the loss of paternally expressed genes). Ghrelin levels in children with PWS are three to four times higher than those in children with standard obesity [37]. Three reviews showed that growth hormone therapy improves muscle mass, speeds up vertical growth, and may even help with cognitive development [15,37,47]. Bardet-Biedl syndrome (BBS) is much rarer (1:100,000–160,000) and was observed in one cohort-based review. Approximately 72–86% of children with BBS develop obesity, usually along with retinal issues, extra fingers or toes, and kidney problems [36].

3.4.3 Hypothalamic Obesity

Three reviews covered hypothalamic obesity, focusing mainly on children who survived craniopharyngioma. The data pointed in the same direction across all three reviews: 25%–60% of children develop obesity after treatment for tumors in the hypothalamic-pituitary region. Weight gain occurs rapidly —usually within 6–12 months—and children gain an average of 10–20 kg in the first year alone [16]. The underlying issue is clear: they have an impaired ability to feel full, their vagal nerve overfires, and they lack normal hormone output. Every single review warned that standard lifestyle and dietary changes fail in these children. Pharmacotherapy (such as GLP-1 receptor agonists or octreotide) barely made a dent in small case studies, indicating that we do not have enough data to make firm recommendations [40].

3.4.4 Medication-Induced Obesity

Three reviews examined this—including two high-quality meta-analyses covering more than 5,000 children. In fact, they found that atypical antipsychotics trigger major weight gain in 15–30% of the children taking them [22,23]. Olanzapine hits the hardest, causing an average gain of 8.5 kg over just 12 weeks. Risperidone follows at 5.3 kg, and quetiapine causes about 4.4 kg of gain [22]. Weight gain occurred fastest during the first 12 weeks, along with major spikes in blood sugar and bad cholesterol. Galling et al. [24] conducted the highest-quality review in our batch (AMSTAR-2: high). They found that children exposed to antipsychotics had a 2.58 odds ratio for developing type 2 diabetes. Because the data aligned so perfectly across all three reviews, this category provided the strongest evidence base.

3.4.5 Endocrine Causes

Two reviews explored endocrine triggers. Both reviews completely agreed that real endocrine causes sit behind less than 1% of childhood obesity cases [8,20]. Cushing syndrome can be identified because the child's vertical growth stalls entirely (children with normal primary obesity usually grow taller). Wide purple stretch marks, weak muscles, and high blood pressure are also observed, and the condition is confirmed by checking cortisol levels in the urine or saliva [20]. Hypothyroidism causes mild weight gain but also stunts vertical growth and bone age. Doctors recommend screening TSH levels strictly in children who are gaining weight while their height stalls [21]. Both reviews scored low to moderate for quality; however, they both strongly advise against universal hormone screening. Doctors should rely entirely on clinical red flags to decide who gets tested.

3.5 Diagnostic Approaches Across Reviews

Reviews consistently advise doctors to watch out for specific clinical red flags before testing for secondary causes [5,8,27,41].

- Severe weight gain starting very early (before age 5, but especially before age 2)
- A rapid, unnatural spike in the child's weight trajectory
- Slowed vertical growth or unusually short stature
- Delays in learning or hitting developmental milestones
- Distinct or unusual facial features
- An extreme, constant hunger that doesn't match the child's body fat levels
- A family tree showing parents who are related (consanguinity)
- Health issues spanning multiple organ systems
- History of a hit to the hypothalamus (e.g., surgery, radiation, or brain tumor)
- A clear timeline linking the weight gain to a new prescription

We developed a clear diagnostic flow chart based on this converging evidence (Figure 5). Table 4 lists the best treatment plans across different categories.

Figure 5. Clinical algorithm for approach to secondary obesity in children: initial assessment for red flags, followed by targeted investigations (genetic testing, endocrine workup, neuroimaging) and diagnosis-specific management pathways. Adapted from converging evidence across included reviews.

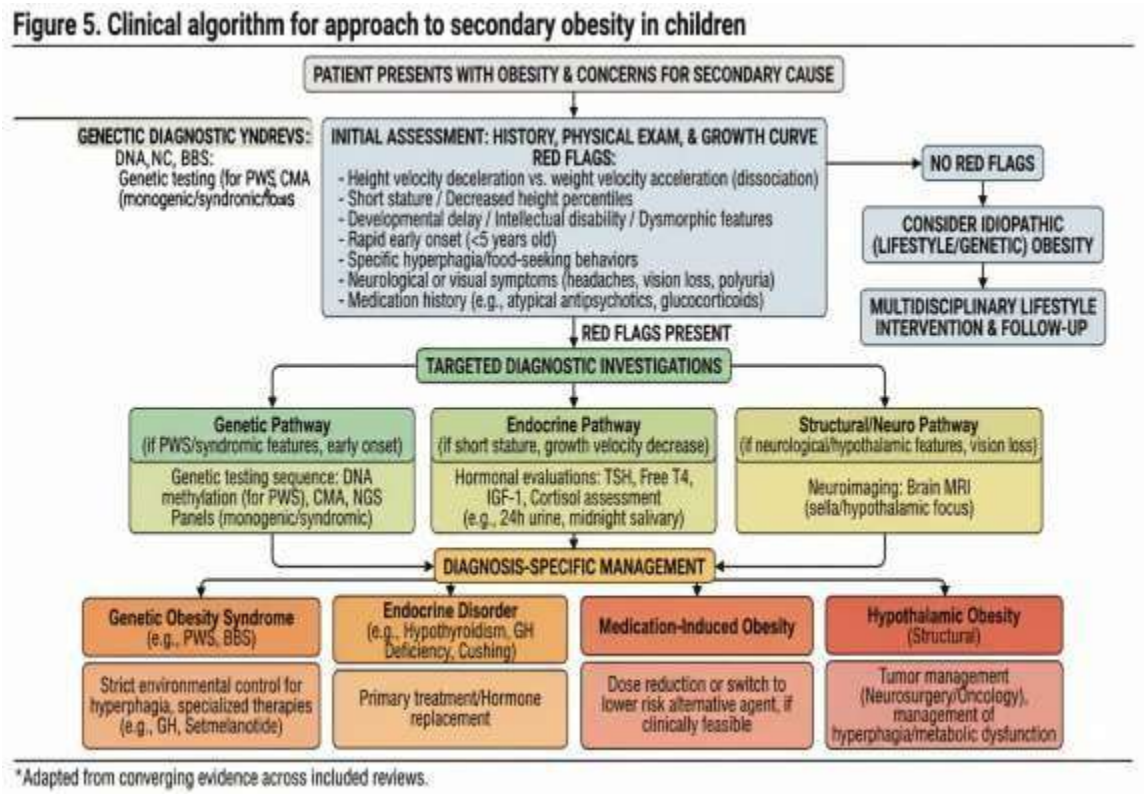


Table 4. Management evidence and quality grading by secondary cause category, synthesized across included reviews.

Category	Intervention	Effect Size / Outcome	No. Reviews Reporting	Evidence Quality	Consistency Across Reviews	Grade
Monogenic Obesity	Setmelanotide (MC4R/POMC/LEPR)	Average weight drops 10–15% in phase 3 trials	2	Moderate	Consistent	B
Monogenic Obesity	Recombinant leptin (leptin deficiency)	Massive weight loss; completely stops the extreme hunger	2	Low	Consistent	B
Genetic Syndromes (PWS)	Growth hormone therapy	Better fat-to-muscle ratios, faster height growth, sharper thinking	3	Moderate	Highly consistent	A
Hypothalamic Obesity	GLP-1 receptor agonists / Octreotide	Slight weight drops; results bounce around from patient to patient	1	Low	Insufficient data	C
Medication-Induced	Switch to weight-neutral agent + metformin	Slows down the weight gain; helps the body respond to insulin	3	Moderate–High	Consistent	B
Endocrine Causes	Hormone replacement / endocrine treatment	Weight normalizes once doctors treat the root problem	1	Low	Consistent (limited data)	B

4. Discussion

4.1 Summary of Evidence

This umbrella review synthesizes evidence from 30 separate papers to provide the highest-order view of secondary childhood obesity currently available. Across all five categories, the data prove that secondary causes account for approximately 5–10% of total childhood obesity. Although this may seem small, these cases matter immensely because the underlying biology differs, they require unique testing, and we have targeted drugs to treat them. We found our strongest evidence when looking at medication-induced obesity (especially weight gain associated with antipsychotics). The meta-analyses for medications were perfectly aligned. We also observed incredibly consistent data supporting the use of growth hormone therapy for children with Prader-Willi syndrome.

The 2020 approval of setmelanotide has changed the landscape for POMC, PCSK1, and LEPR deficiencies. Patients lost an average of 10%–15% of their body weight in the large phase 3 trials [30,31]. Administration of recombinant leptin to children born without it triggers massive, life-saving weight loss [11]. These reviews repeatedly highlight the importance of running genetic tests on children who develop severe obesity early in life. You will find a distinct genetic cause in about 10% of those kids [41].

4.2 Consistency and Heterogeneity Across Reviews

The main reason to conduct an umbrella review is to determine whether the separate studies agree with each other. In our case, the data matched perfectly when looking at medication-induced weight gain, Prader-Willi syndrome, and overall prevalence rates. The data on monogenic obesity aligned moderately well, although the prevalence estimates fluctuated between 2% and 10%, depending on the severity of the patients' condition and the type of genetic testing used by the doctors. The evidence completely fell apart for hypothalamic obesity. We found only three reviews on this topic, and because no proper randomized trials have been conducted, we can n not make strong treatment recommendations yet.

Notably, we observed a moderate overlap in the citations for the medication reviews (CCA 12–18%). This means that they shared some of the same primary studies, but each review still brought unique data to the table. Genetic reviews shared almost no citations, indicating that they built their conclusions on entirely different patient groups.

4.3 Clinical Implications

This umbrella review provides doctors with a solid cheat sheet for diagnosing secondary obesity. Multiple reviews point to the exact same red-flag features, which completely supports the use of a structured clinical algorithm (see Figure 5). Doctors should order genetic tests immediately for any child who develops severe obesity early on (especially before the age of 5), and double that urgency if the child is constantly hungry, falling behind in school, or has parents who are closely related [41]. Doctors should only check hormones when they observe specific physical signs; universal hormone screening is a waste of time. Finally, doctors must track the weight and blood sugar of any child taking an atypical antipsychotic and should start with the lowest-risk drug possible [22,24].

All reviews agreed that treatment requires a full medical team. Endocrinologists, geneticists, dietitians, psychologists, and neurologists must communicate with each other. Families dealing with inherited genetic defects absolutely need genetic counseling so that they can test other family members [12].

4.4 Limitations

To be fair, the overall quality of the included reviews varied considerably (AMSTAR-2 flagged 30% of them as low confidence). This makes it harder to trust each estimate. Second, most of the papers came from wealthy countries; therefore, the numbers may differ significantly in low-income areas. Third, publication bias definitely skews the numbers. Journals favor publishing new genetic discoveries and positive drug trials, which inflates the literature. Fourth, because some reviews cited the same primary papers, we probably counted a few patient groups more than once when adding up prevalence totals. Fifth, genetic testing improves every year; therefore, the older reviews in our batch

probably undercounted the real number of genetic cases. Finally, we lack long-term outcome data for the newest weight-loss drugs.

4.5 Future Research Priorities

When you look across all 30 reviews, you can clearly see a few major gaps in the research. We urgently need:

1. Real-world epidemiological studies tracking secondary obesity across different geographic and economic zones.
2. Fresh trials to test and validate clinical red-flag checklists.
3. Studies tracking the long-term natural history of newly discovered genetic variants.
4. Proper randomized controlled trials testing GLP-1 receptor agonists for hypothalamic obesity.
5. Research on the best ways to integrate fast genetic testing into everyday pediatric clinics.
6. Clear economic analyses to figure out if these highly targeted drugs are cost-effective.
7. Studies on the psychological toll of informing a child of a permanent genetic obesity diagnosis.

5. Conclusions

We developed this umbrella review to synthesize the highest level of evidence on every major category of secondary childhood obesity. That said, secondary causes still account for 5–10% of childhood obesity. They demand highly specific medical attention because the underlying biology, diagnostic criteria, and available drugs differ from those for standard obesity. The data tracking antipsychotic weight gain and growth hormone therapy for Prader-Willi syndrome are robust and consistent. Sadly, the evidence for treating hypothalamic obesity remains terribly thin. A strict red-flag checklist should be used by doctors, and appropriate early genetic tests should be ordered and treatment plans developed based on the specific root cause if converging evidence is available. We desperately need fresh umbrella reviews moving forward to track long-term drug outcomes as genomic medicine gets better.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding

No specific funding was received for this umbrella review.

Author Contributions

All authors contributed to the study design, selection, quality appraisal, data extraction, synthesis, and manuscript preparation. All authors have approved the final version of the manuscript.

Ethical Approval

Not applicable (umbrella review of published literature).

References

1. World Health Organization. Obesity and overweight [Internet]. Geneva: WHO; 2021 [cited 2025 Oct 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Swinburn BA, Kraak VI, Allender S, et al. The global syndemic of obesity, undernutrition, and climate change. Lancet. 2019;393(10173):791–846.
4. Lobstein T, Jackson-Leach R, Moodie ML, et al. Child and adolescent obesity: part of a bigger picture. Lancet. 2015;385(9986):2510–20.
5. Sahoo K, Sahoo B, Choudhury AK, Sofi NY, Kumar R, Bhadoria AS. Childhood obesity: causes and consequences. J Family Med Prim Care. 2015;4(2):187–92.
6. Styne DM, Arslanian SA, Connor EL, et al. Pediatric obesity — assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(3):709–57.
7. Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci. 2013;1281(1):123–40.

8. Styne DM, et al. Pediatric obesity assessment, treatment, and prevention. J Clin Endocrinol Metab. 2017;102(3):709–57.
10. Yeo GSH, Heisler LK. Unraveling the brain regulation of appetite: lessons from genetics. Nat Neurosci. 2012;15(10):1343–9.
11. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997;387(6636):903–8.
12. Albuquerque D, Stice E, Rodríguez-López R, Manco L, Nóbrega C. Current review of genetics of human obesity: from molecular mechanisms to an evolutionary perspective. Mol Genet Genomics. 2015;290(4):1191–221.
13. Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics. 2001;108(5):E92.
14. Butler MG, Manzardo AM, Forster JL. Prader-Willi syndrome: clinical genetics and diagnostic aspects with treatment approaches. Curr Pediatr Rev. 2016;12(2):136–66.
15. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocr Rev. 2007;28(2):219–51.
16. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2003;88(6):2586–92.
17. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404(6778):661–71.
18. Roth CL, Enriori PJ, Harz K, et al. Peptide YY is a regulator of energy homeostasis in obese children before and after weight loss. J Clin Endocrinol Metab. 2005;90(12):6386–91.
19. Müller HL, Gebhardt U, Schroder S, et al. Analyses of treatment variables for patients with childhood craniopharyngioma. Neurosurgery. 2010;67(2):398–408.
20. Lodish M. Genetics of adrenocortical development and tumors. Endocrinol Metab Clin North Am. 2017;46(2):419–33.
21. Reinehr T. Obesity and thyroid function. Mol Cell Endocrinol. 2010;316(2):165–71.
22. Correll CU, Manu P, Olshansky V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302(16):1765–73.
23. Bonnot O, Inausti-Piquer L, Minoletti A. Metabolic side-effects of antipsychotic medication in children: a systematic review and meta-analysis. Bipolar Disord. 2011;(Suppl).
24. Galling B, Roldn A, Nielsen RE, et al. Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. JAMA Psychiatry. 2016;73(3):247–59.
25. Yanovski JA, Yanovski SZ. Treatment of pediatric and adolescent obesity. JAMA. 2003;289(14):1851–3.
26. Reinehr T, Hinney A, de Sousa G, et al. Definable somatic disorders in overweight children and adolescents. J Pediatr. 2007;150(6):618–22.
27. Speiser PW, Rudolf MC, Anhalt H, et al. Childhood obesity. J Clin Endocrinol Metab. 2005;90(3):1871–87.
28. Hebebrand J, Volckmar AL, Knoll N, Hinny A. Chipping away the 'missing heritability': GIANT steps forward in the molecular elucidation of obesity. Obes Facts. 2010;3(5):294–303.
29. Iughetti L, China M, Berri R, Predieri B. Pharmacological treatment of obesity in children and adolescents: present and future. J Obes. 2011;2011:928165.
30. Wabitsch M, Funcke JB, Lennerz B, et al. Biologically inactive leptin and early-onset extreme obesity. N Engl J Med. 2015;372(1):48–54.
31. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency. Lancet Diabetes Endocrinol. 2020;8(12):960–70.
32. Inge TH, Courcoulas AP, Jenkins TM, et al. Weight loss and health status 3 years after bariatric surgery in adolescents. N Engl J Med. 2016;374(2):113–23.
33. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
34. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

35. Farooqi IS, Yeo GS, Keogh JM, et al. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest. 2000;106(2):271–9.
36. Bardet-Biedl Syndrome Research Consortium. Bardet-Biedl syndrome: phenotypic characterization of a multi-centre cohort. Arch Dis Child. 2003;88(8):708–13.
37. Haqq AM, Farooqi IS, O'Rahilly S, et al. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. J Clin Endocrinol Metab. 2003;88(1):174–8.
38. Cohen MM Jr. Mental deficiency, alterations in performance, and CNS abnormalities in over-weight children. Clin Genet. 2005;68(2):93–105.
39. Clément K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392(6674):398–401.
40. Mameli C, Mazzantini S, Zuccotti GV. Nutrition in the first 1000 days: the origin of childhood obesity. Int J Environ Res Public Health. 2016;13(9):838.
41. Kleinendorst L, Massink MPG, Cooiman MI, et al. Genetic obesity: next-generation sequencing results of 1230 patients with obesity. J Med Genet. 2018;55(9):578–86.
42. Martos-Moreno GÁ, Chowen JA, Argente J. Metabolic signals in human puberty: effects of over and undernutrition. Mol Cell Endocrinol. 2010;324(1–2):70–81.
43. Garg S, Agarwal S. Pharmacological treatment of obesity in children and adolescents. Indian Pediatr. 2012;49(11):903–12.
44. Martínez Aguayo A, Aglony M, Bancalari R, et al. Birth size, infant weight gain, and adrenal and gonadal hormone levels in prepubertal children. Clin Endocrinol (Oxf). 2012;76(4):572–9.
45. Yazdi FT, Clee SM, Meyre D. Obesity genetics in mouse and human: back and forth, and back again. PeerJ. 2015;3:e856.
46. Hebebrand J, Hinney A. Environmental and genetic risk factors in obesity. Child Adolesc Psychiatr Clin N Am. 2009;18(1):83–94.
47. Fintini D, Cianfarani S, Cofini M, et al. The bones of children with obesity. Front Endocrinol (Lausanne). 2020;11:200.
48. Müller HL, Emser A, Faldum A, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. J Clin Endocrinol Metab. 2004;89(7):3298–305.
49. Censani M, Orsso CE, Butler MG. The Prader-Willi syndrome and related disorders. Pediatr Endocrinol Rev. 2018;16(1):42–56.