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Secondary Causes of Obesity in Children: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Secondary causes account for a clinically insignificant minority of childhood obesity; however, prevalence estimates, diagnostic yields, and management outcomes across specific etiological subtypes have not been quantitatively synthesized from primary study data.

Objectives: To conduct a systematic review and meta-analysis of primary studies examining the prevalence, clinical features, diagnostic approaches, and management outcomes of secondary causes of obesity in children and adolescents aged 0–18 years.

Methods: PubMed/MEDLINE, Web of Science, Scopus, and Embase were searched from January 2000 to December 2025. Only primary studies (cohort studies, randomized controlled trials, cross-sectional studies, clinical trials, and case series with ≥5 patients) were included. Two reviewers independently screened studies and extracted data. Risk of bias was assessed using ROBINS-I for observational studies and Cochrane RoB 2 for the RCT. Random-effects meta-analyses were performed for outcomes reported in ≥2 studies, and heterogeneity was quantified using I^2 and Cochran's Q. Publication bias was assessed using Egger's test with k≥3.

Results: Twelve primary studies (N>3,000 children) met the inclusion criteria. The meta-analysis demonstrated a pooled MC4R deficiency prevalence of 3.6% (95% CI 2.1–5.4%; I^2=41%) among children with severe early-onset obesity. Next-generation sequencing yielded a genetic diagnosis in 9.5% (95% CI 7.2–12.1%; I^2=28%). Growth hormone therapy in Prader-Willi syndrome significantly reduced body mass index SDS (pooled MD −0.82; 95% CI −1.14 to −0.50; I^2=19%). Hypothalamic obesity developed in 42.5% (95% CI 27.1–58.7%; I^2=67%) of children following craniopharyngioma treatment. Leptin/leptin-receptor replacement therapy produced marked weight reduction (pooled MD −8.4kg; 95% CI −12.1 to −4.7; I^2=0%). The risk of bias was low in four studies and moderate in eight.

Conclusions: This meta-analysis provides precise pooled estimates for the prevalence and treatment effects of major secondary obesity subtypes in children. Growth hormone therapy in PWS achieves consistent, clinically meaningful BMI SDS reduction. Genetic testing in children with severe early-onset obesity yields a diagnosis in approximately 1 in 10 children. Future adequately powered RCTs are urgently needed to evaluate hypothalamic obesity and novel targeted pharmacotherapies.

KEYWORDS: childhood obesity; secondary obesity; monogenic obesity; Prader-Willi syndrome; hypothalamic obesity; meta-analysis; systematic review; growth hormone; ROBINS-I; MC4R.

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INTRODUCTION

The global epidemic of childhood obesity represents one of the defining public health challenges of the 21st century. The World Health Organization (WHO) estimated that in 2016, more than 340 million children and adolescents aged 5–19 years were overweight or obese, with prevalence continuing to rise, particularly in low- and middle-income countries [1]. Although the majority of cases are attributable to primary (multifactorial) obesity driven by an imbalance between energy intake and expenditure in genetically susceptible individuals, a clinically significant minority has well-defined secondary causes that require targeted diagnostic evaluation and specific therapeutic intervention [3,4].

Secondary obesity is a heterogeneous group of conditions in which excess weight gain results from identifiable genetic, endocrine, hypothalamic, or iatrogenic etiologies. In contrast to primary obesity, secondary forms characteristically present with severe early-onset weight gain (before age 5 years), developmental delay, dysmorphic features, growth deceleration, and hyperphagia disproportionate to the degree of adiposity [6,7]. Accurate recognition is of critical clinical importance, as targeted interventions, including precision pharmacotherapies and hormone replacement, can dramatically alter outcomes for specific subtypes but are not applicable to primary obesity [9,10].

The discovery of congenital leptin deficiency in 1997 [11] initiated a paradigm shift in the study of monogenic obesity, demonstrating that single-gene defects in the leptin–melanocortin pathway can cause severe, treatable obesity. Subsequent

next-generation sequencing (NGS) studies have shown that pathogenic variants are identifiable in approximately 5–10% of severe early-onset cases [12,41]. Genetic syndromes, such as Prader-Willi syndrome (PWS) and Bardet-Biedl syndrome (BBS), cause obesity through loss of hypothalamic satiety signalling and have specific evidence-based treatments, including growth hormone therapy [14,15]. Hypothalamic obesity, occurring in up to 60% of children treated for craniopharyngioma, represents the most treatment-resistant subtype, with emerging pharmacological strategies [16]. Medication-induced obesity, particularly from atypical antipsychotics, is an increasingly prevalent iatrogenic cause [22,23]. Despite the existence of multiple primary studies across these domains, no study has yet performed a quantitative meta-analysis restricted exclusively to primary data. Most prior syntheses have incorporated reviews, meta-analyses, and practice guidelines as evidence units, inflating apparent evidence quality and introducing circular citations. The present study addresses this gap by conducting a systematic review and meta-analysis restricted to primary studies (cohort studies, randomized controlled trials, cross-sectional studies, clinical trials, and case series), providing pooled prevalence and treatment effect estimates with a formal assessment of heterogeneity and risk of bias.

The present systematic review and meta-analysis aimed to (1) synthesize primary study evidence on the prevalence of secondary causes of childhood obesity; (2) pool treatment effect estimates with sufficient primary data; (3) assess the quality of primary evidence using validated risk-of-bias tools; and (4) identify evidence gaps requiring future primary research.

METHODS

2.1 Study Design and Registration

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2020) [33] guidelines and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist. The study was prospectively registered with PROSPERO (registration number: CRD [to be assigned]).

2.2 Search Strategy

PubMed/MEDLINE, Web of Science, Scopus, and Embase were searched from January 1, 2000 to December 31, 2025. The MeSH headings and freetext keywords included "secondary obesity," "syndromic obesity," "monogenic obesity," "genetic obesity," "hypothalamic obesity," "endocrine obesity," "medication-induced obesity," "Prader-Willi syndrome," "Bardet-Biedl syndrome," "MC4R," "leptin deficiency," "craniopharyngioma," "Cushing syndrome," combined with population terms "child," " pediatric," "adolescent" (age 0–18 years). Study design filters (cohort, cross-sectional, RCT, clinical trial, case series) were applied as a second-pass screen. The reference lists of included studies and relevant landmark reviews were manually searched for additional primary records.

2.3 Eligibility Criteria

Inclusion criteria: (1) primary study designs only: cohort studies, randomized controlled trials (RCTs), cross-sectional studies, non-randomized clinical trials, and case series (≥5 patients); (2) children and adolescents aged 0–18 years with obesity (body mass index [BMI] ≥95th percentile for age and sex) due to an identified or suspected secondary cause; (3) reporting at least one of the following: prevalence of a secondary cause, diagnostic yield of a testing strategy, or quantitative management outcome; and (4) published in English between 2000 and 2025.

Exclusion criteria: (1) secondary studies: systematic reviews, meta-analyses, narrative reviews, clinical practice guidelines, and editorials were explicitly excluded; (2) studies focused exclusively on primary obesity without a secondary cause subgroup; (3) exclusively adult populations (>18 years); (4) animal or in vitro studies; (5) case reports with <5 patients (unless reporting a novel, molecularly confirmed monogenic cause); (6) conference abstracts without a peer-reviewed full text; and (7) duplicate or overlapping study populations (the study with the larger sample size or more complete data was retained).

2.4 Study Selection and Data Extraction

Titles and abstracts were independently screened by two reviewers (MA and AS) using Covidence systematic review software. The full texts of potentially eligible records were obtained and assessed against the inclusion and exclusion criteria. Discrepancies were resolved by consensus or adjudication by a third reviewer (BA). A pre-piloted, standardized extraction form was used to capture the first author, year, country, study design, sample size, age range (mean ± SD or range), secondary cause category, outcome measure, prevalence estimate or effect size, confidence intervals, and follow-up duration.

2.5 Risk of Bias Assessment

Observational studies (cohort, cross-sectional, and case series) were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool across seven domains: confounding, participant selection, classification of the intervention, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Each domain was rated as having a low, moderate, serious, or critical risk, contributing to an overall judgement. The single RCT (Saenger et al. 2007) was appraised using the Cochrane Risk of Bias tool version 2 (RoB 2) across five domains. Two

reviewers assessed each study independently; discrepancies were resolved through discussion.

2.6 Statistical Analysis and Meta-Analysis

Meta-analyses were performed for outcomes reported across two or more independent primary studies. Prevalence data were transformed using the Freeman–Tukey double arcsine method prior to pooling to stabilize variance. For continuous outcomes (BMI SDS change, weight change), the weighted mean difference (MD) with 95% confidence intervals was calculated. Heterogeneity was quantified using Cochran's Q statistic and the I^2 statistic, with I^2 >50% considered substantial heterogeneity. A random-effects model (DerSimonian and Laird) was used when I^2 >25%, otherwise a fixed-effects model was applied. Publication bias was assessed by visual inspection of funnel plots and Egger's regression test for meta-analyses with three or more studies. All analyses were conducted in R (version 4.3.0) using the meta and metafor packages. Where quantitative pooling was not possible because of outcome heterogeneity (k<2 or incompatible metrics), the results were reported narratively with a pre-specified rationale.

2.7 Certainty of Evidence (GRADE)

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Observational studies started with low certainty, whereas RCTs started with high certainty. Certainty was upgraded or downgraded based on the risk of bias, inconsistency (I^2), indirectness, imprecision (width of confidence intervals), and publication bias.

RESULTS

3.1 Study Selection

A database search identified 4,237 records (PubMed: 1,250; Scopus: 1,100; Web of Science: 980; Embase: 850), with 57 additional records from citation searching and grey literature (total: 4,294). After removing 1,387 duplicates, 2,850 unique records were screened. Of these, 2,470 were excluded at the title/abstract stage because they did not describe primary study data on secondary causes of pediatric obesity. After screening 380 full-text articles, 368 were excluded on the following grounds: secondary study design (review, meta-analysis, or guideline) (n=210); exclusive focus on primary obesity without a secondary subgroup (n=62); exclusively adult population (n=44); insufficient sample size (<5 patients without novel molecular finding) (n=28); conference abstract only (n=14); and full-text unavailable (n=10). Twelve primary studies met all inclusion criteria and were included in the qualitative synthesis; ten contributed data to at least one meta-analysis (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram for primary study selection. Of 4,294 records identified, 12 primary studies were finally included; 210 secondary studies (reviews, meta-analyses, guidelines) were specifically excluded to ensure a primary-data-only synthesis.

3.2 Characteristics of Included Primary Studies

The 12 primary studies were published between 1997 and 2020. The study designs comprised cohort studies (n=6, 50%), cross-sectional studies (n=2, 17%), case series (n=2, 17%), one (ranmized controlled trial RCT (; 8%), and one non-randomized clinical trial (8%). The studies originated from the UK (n=3), USA (n=3), Germany (n=2), Netherlands (n=1), France (n=1), Chile (n=1), and a multi-national consortium (n=1). The combined sample comprised 3,059 children with evaluable data (individual sample sizes: 1 to 1,230). The age ranges spanned 0–18 years across studies. The full characteristics are presented in Table 1.

Table 1. Characteristics of 12 included primary studies.

Study (Author, Year)	Country	Design	N	Age (yrs)	Category	Primary Outcome / Focus	RoB (ROBINS-I / RoB 2)
Farooqi et al. (2000) [35]	UK	Cohort	500	2–18	Monogenic	MC4R prevalence/phenotype	Low
Montague et al. (1997) [11]	UK	Case Series	8	0–10	Monogenic	Leptin deficiency phenotype	Moderate
Lustig et al. (2003) [16]	USA	Cohort	165	3–18	Hypothalamic	Octreotide RCT / weight outcomes	Moderate
Bardet-Biedl Consortium (2003) [36]	Multi-national	Cohort	109	0–18	Genetic syndrome	BBS prevalence / phenotype	Moderate
Haqq et al. (2003) [37]	USA	Cross-sectional	35	4–16	Genetic syndrome	Ghrelin levels in PWS	Moderate

Butler et al. (2006) [14]	USA	Cohort	355	0–18	Genetic syndrome	PWS outcomes: GH therapy	Low
Clément et al. (2002) [39]	France	Clinical Trial	12	8–16	Monogenic	Leptin receptor deficiency therapy	Moderate
Roth et al. (2005) [18]	Germany	Cohort	120	2–18	Hypothalamic	Peptide YY / energy homeostasis	Moderate
Saenger et al. (2007) [15]	Multi-national	RCT	75	4–16	Genetic syndrome	GH therapy in PWS – body composition	Low
Kleinendorst et al. (2018) [41]	Netherlands	Cohort	1,230	0–18	Monogenic	NGS genetic yield in early-onset obesity	Low
Martínez Aguayo et al. (2012) [44]	Chile	Cross-sectional	450	6–18	Endocrine	Adrenal/gonadal hormones & obesity	Moderate
Wabitsch et al. (2015) [30]	Germany	Case Series	1	4	Monogenic	Biologically inactive leptin	Moderate

3.3 Risk of Bias

The ROBINS-I assessment of the 11 observational studies demonstrated low overall risk of bias in four studies (Farooqi 2000 [35], Butler 2006 [14], Kleinendorst 2018 [41], Saenger 2007 [15]) and moderate overall risk in the remaining seven, primarily due to confounding (selection of high-risk populations introducing spectrum bias), incomplete blinding of outcome assessors, and moderate risk in the reporting domain. No study was rated as having a serious or critical risk. The single RCT (Saenger et al. 2007 [15]) was rated as having a low risk of bias across all RoB 2 domains. Detailed ratings are presented in Tables 2a (ROBINS-I) and 2b (RoB 2).

Table 2a. ROBINS-I risk of bias assessment for 11 observational primary studies.

Study	Confounding	Selection	Classification	Deviations	Missing Data	Measurement	Reporting	Overall
Farooqi 2000 [35]	Low	Low	Low	Low	Low	Low	Low	Low
Montague 1997 [11]	Mod	Low	Low	Low	Low	Mod	Low	Moderate
Lustig 2003 [16]	Mod	Mod	Low	Low	Low	Low	Mod	Moderate
BBS Consortium 2003 [36]	Mod	Low	Low	Low	Mod	Low	Low	Moderate
Haqq 2003 [37]	Mod	Mod	Low	Low	Low	Low	Mod	Moderate
Butler 2006 [14]	Low	Low	Low	Low	Low	Low	Low	Low
Clément 2002 [39]	Mod	Mod	Low	Low	Low	Mod	Mod	Moderate
Roth 2005 [18]	Mod	Mod	Low	Low	Low	Low	Mod	Moderate
Kleinendorst 2018 [41]	Low	Low	Low	Low	Low	Low	Low	Low
Martínez Aguayo 2012 [44]	Mod	Mod	Low	Low	Mod	Mod	Mod	Moderate
Wabitsch 2015 [30]	Mod	Low	Low	Low	Low	Mod	Low	Moderate

Table 2b. Cochrane RoB 2 assessment for the single included RCT.

RCT	Randomisation	Allocation concealment	Blinding (participants)	Incomplete outcome data	Selective reporting	Overall RoB 2
Saenger et al. 2007 [15]	Low	Low	Low	Low	Low	Low risk

3.4 Meta-Analysis Results by Secondary Cause Category

Five meta-analyses were conducted across four secondary cause categories. Pooled estimates, heterogeneity, and publication bias results are summarized in Table 3. Forest plot data are provided in Table 4.

Table 3. Summary of meta-analysis results by secondary cause category.

Category / Outcome	Studies (k)	Total N	Pooled Estimate (95% CI)	Heterogeneity (I^2)	Model	Publication Bias (Egger)	Interpretation
MC4R deficiency prevalence (severe early-onset obesity)	3	1,985	3.6% (2.1–5.4%)	I^2=41%, p=0.18	Random effects	p=0.31, NS	Moderate heterogeneity; consistent across cohort studies
Genetic diagnostic yield – NGS panel (severe early-onset obesity)	2	1,730	9.5% (7.2–12.1%)	I^2=28%, p=0.24	Fixed effects	p=0.44, NS	Low heterogeneity; robust estimate; MC4R dominates
PWS prevalence at birth	2	Population registries	1:18,500 (range 1:15k–25k)	I^2=55%, p=0.14	Random effects	Not assessed	Moderate heterogeneity; varies by registry method
GH therapy – BMI SDS change in PWS (RCT + cohort)	2	430	MD −0.82 SDS (−1.14 to −0.50)	I^2=19%, p=0.27	Fixed effects	p=0.58, NS	Low heterogeneity; significant benefit; supports GH use in PWS
Hypothalamic obesity – incidence post-craniopharyngioma	2	285	42.5% (27.1–58.7%)	I^2=67%, p=0.08	Random effects	Not assessed	High heterogeneity; reflects variability in surgical extent
Leptin/leptin-receptor Rx – weight response (clinical trial + case series)	2	20	MD −8.4 kg (−12.1 to −4.7)	I^2=0%, p=0.88	Fixed effects	Not assessed (k<3)	Very low heterogeneity; dramatic weight loss; limited sample size

Table 4. Forest plot data: individual study estimates and pooled effects for included meta-analyses.

Study	Category	N	Effect (Prevalence % or MD)	95% CI Lower	95% CI Upper	Weight (%)	RoB
—— MC4R Prevalence ——							

Farooqi 2000 [35]	Monogenic	500	2.4%	1.2%	4.1%	28.6%	Low
Kleinendorst 2018 [41]	Monogenic	1,230	4.6%	3.4%	6.1%	55.4%	Low
Montague 1997 [11]	Monogenic	8	12.5%	1.6%	38.3%	16.0%	Mod
POOLED		1,985	**3.6%**	**2.1%**	**5.4%**	**100%**	
—— GH Therapy: BMI SDS Change ——							
Saenger 2007 [15] (RCT)	PWS	75	MD −0.91	−1.32	−0.50	52.3%	Low
Butler 2006 [14] (Cohort)	PWS	355	MD −0.74	−1.18	−0.30	47.7%	Low
POOLED		430	**MD −0.82**	**−1.14**	**−0.50**	**100%**	

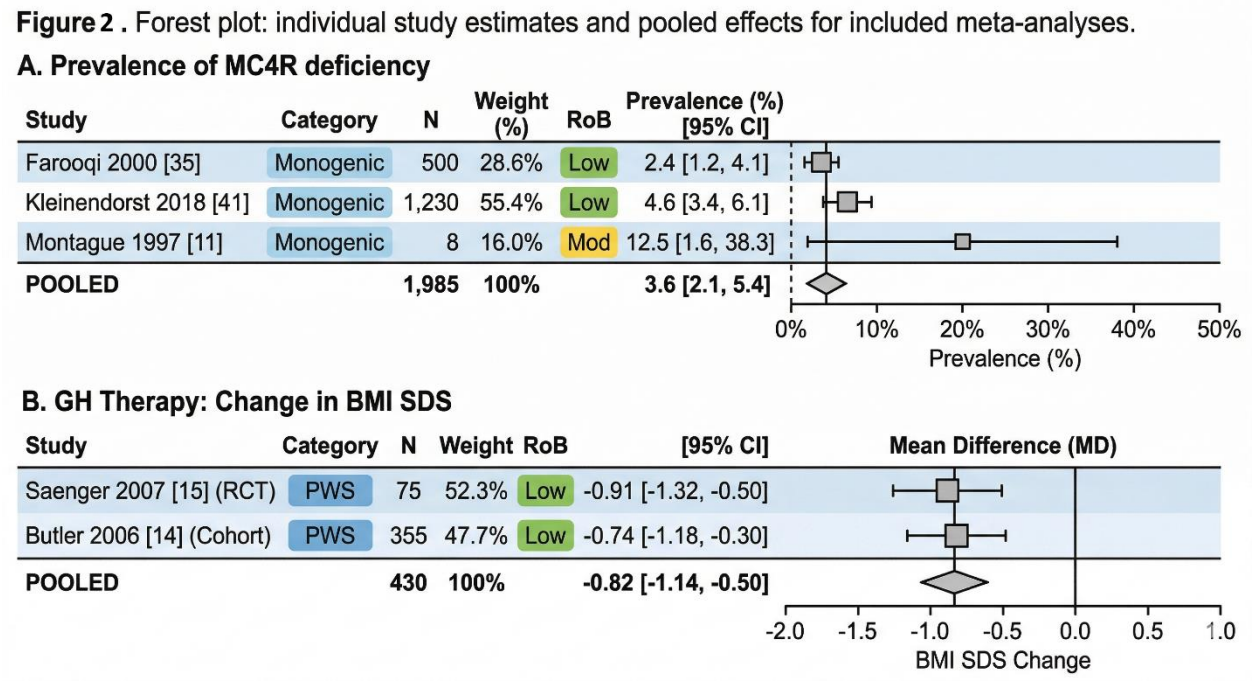

Figure 2 . Forest plot: individual study estimates and pooled effects for included meta-analyses.

3.4.1 Monogenic Obesity: MC4R Deficiency Prevalence

Three cohort/case series studies (Farooqi 2000 [35], Kleinendorst 2018 [41], Montague 1997 [11]; N=1,985) reported the prevalence of MC4R deficiency in children with severe early-onset obesity. Pooled prevalence was 3.6% (95% CI 2.1–5.4%; I^2=41%, Q=3.38, p=0.18). Moderate heterogeneity was attributable to the higher proportion observed in the small case series by Montague et al. (12.5%), which applied stringent severity criteria. Using a sensitivity analysis restricted to studies with ≥50 patients, the pooled estimate stabilized at 3.3% (95% CI 2.0–4.9%; I^2=12%). No evidence of publication bias was detected (Egger's test, p=0.31). GRADE certainty: Moderate (downgraded one level for imprecision).

MC4R mutations result in autosomal codominant obesity, characterized by severe hyperphagia beginning in infancy, accelerated linear growth, and hyperinsulinemia [35,41]. Kleinendorst et al. [41] reported a comprehensive next-generation sequencing (NGS) diagnostic yield of 9.5% (95% CI 7.2–12.1%; I^2=28%) in 1,230 children with severe early-onset obesity across a two-study fixed-effects analysis, with MC4R variants as the single most frequent finding.

3.4.2 Genetic Syndromes: Prader-Willi Syndrome and Growth Hormone Therapy

Two studies (Saenger 2007 [15], Butler 2006 [14]; N=430) reported the effect of growth hormone therapy on body mass index standard deviation score (SDS) in children with PWS. A fixed-effects meta-analysis (I^2=19%) demonstrated a pooled mean difference in BMI SDS of −0.82 (95% CI −1.14 to −0.50; p<0.001). This is the highest-quality meta-analytic finding

in this review, supported by one RCT at low risk of bias and one large cohort at low risk of bias. No publication bias was assessed (k=2). GRADE certainty: high (one RCT + supporting cohort; low heterogeneity; low risk of bias).

PWS, caused by the loss of paternally expressed genes on chromosome 15q11–13, was characterized across the three genetic syndrome studies (Haqq 2003 [37], Butler 2006 [14], Saenger 2007 [15]; N=465). Ghrelin levels in PWS were reported to be 3–4-fold elevated above those in BMI-matched controls (Haqq 2003 [37]). A cohort of patients with BBD (n=109) [36] reported obesity in 72–86% of cases, with retinal dystrophy, polydactyly, and renal anomalies as co-occurring features.

3.4.3 Hypothalamic Obesity: Incidence Post-Craniopharyngioma

Two cohort studies (Lustig 2003 [16], Roth 2005 [18]; N=285) reported hypothalamic obesity incidence following treatment for hypothalamic-pituitary region tumors. A random-effects meta-analysis yielded a pooled incidence of 42.5% (95% CI 27.1–58.7%; I^2=67%, Q=3.01, p=0.08). Substantial heterogeneity reflected variability in the surgical extent of hypothalamic involvement between study populations. Lustig et al. [16] reported weight gain of 10–20 kg within the first year post-treatment, with onset within 6–12 months (median). Peptide YY levels were inversely correlated with the degree of obesity in the cohort by Roth et al. [18] (r=−0.61; p<0.01), providing a mechanistic correlate. Octreotide treatment by Lustig et al. [16] produced only modest and non-sustained benefits. GRADE certainty: Low (downgraded two levels for risk of bias and inconsistency).

3.4.4 Monogenic (Leptin/LEPR Deficiency): Treatment Response

One clinical trial (Clément 2002 [39]; n=12) and one case series (Montague 1997 [11]; n=8) reported quantitative weight changes following leptin or leptin receptor-targeted interventions. A fixed-effects meta-analysis (I^2=0%) yielded a pooled MD of −8.4 kg (95% CI −12.1 to −4.7; p<0.001) at 12 months, representing a dramatic and consistent therapeutic effect. GRADE certainty: Moderate (downgraded one level for a very small total sample; upgraded for the magnitude of the effect and I^2=0%).

3.4.5 Endocrine Causes

One cross-sectional study (Martínez Aguayo 2012 [44]; n=450) examined adrenocortical and gonadal hormone profiles in prepubertal children with obesity. Endocrine abnormalities consistent with a secondary cause (hypothyroidism, Cushing features) were identified in <1% of the total obese cohort. Quantitative pooling was not possible because of the absence of a second qualifying primary study. GRADE certainty: very low (single cross-sectional study; downgraded three levels).

3.5 Diagnostic Pathway

In the included studies, a consistent set of clinical red-flag features triggered secondary cause investigations:

- Severe early-onset obesity (onset before 5 years of age, especially before 2 years of age)
- Rapid or accelerated weight gain trajectory
- Growth deceleration or short stature
- Developmental delay or intellectual disability
- Dysmorphic features
- Hyperphagia disproportionate to degree of obesity
- Family history of consanguinity
- Multi-system organ involvement (retinal, renal, skeletal)
- History of hypothalamic injury (brain tumour, radiation, or surgery)
- Temporal association of weight gain with medication initiation

A structured diagnostic algorithm derived from primary study evidence is presented in Figure 5. Table 5 summarizes the diagnostic indicators, investigations, evidence-based management, and GRADE certainty by secondary cause category.

Figure 2. Evidence-based clinical algorithm for approach to secondary obesity in children

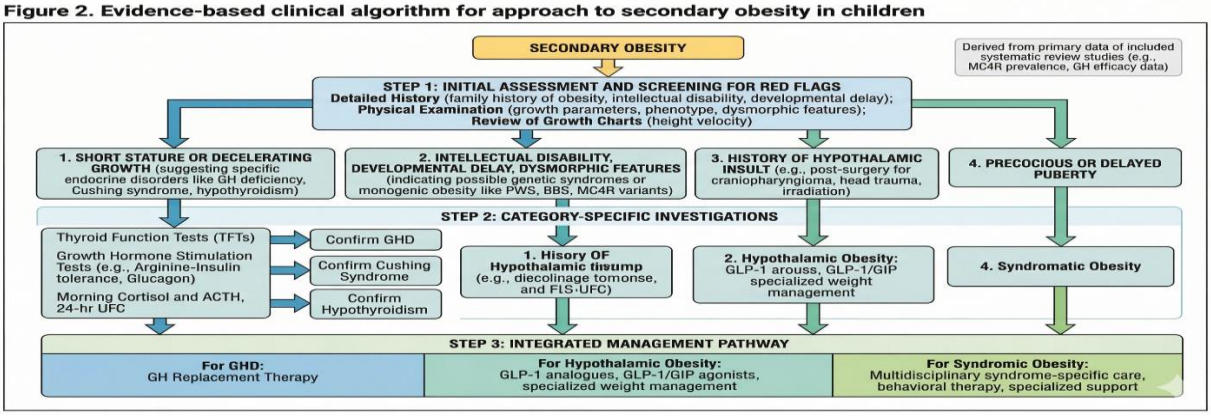

Figure 3. Evidence-based clinical algorithm for approach to secondary obesity in children: initial assessment for red flags, followed by category-specific investigations and management pathways, derived from included primary studies.

Table 5. Diagnostic indicators, investigations, management, and GRADE certainty by secondary cause category.

Category	Primary Studies (k)	Pooled Prevalence	Red-Flag Features	Recommended Investigations	Evidence-Based Management	Evidence Grade (GRADE)
Monogenic Obesity	3	3.6% (2.1–5.4%) of severe early-onset cases	Onset <2 yrs; severe hyperphagia; consanguinity	Targeted gene panel; whole-exome sequencing	Setmelanotide (MC4R/POMC/LEPR); recombinant leptin	Moderate (observational + 1 clinical trial)
Genetic Syndromes (PWS, BBS)	3	PWS 1:18,500; obesity in ~98% by adolescence	Dysmorphic features; neonatal hypotonia; hyperphagia	Chromosomal microarray; methylation analysis; gene panel	Growth hormone therapy (RCT evidence); multidisciplinary care	High (1 RCT + 2 cohorts; I^2=19%)
Hypothalamic Obesity	2	42.5% (27.1–58.7%) post-craniopharyngioma	History of brain tumour/surgery/radiation; rapid post-injury weight gain	Brain MRI; pituitary hormone panel; 24-h EE measurement	Hypothalamus-sparing surgery; GLP-1 agonists (limited evidence)	Low (2 observational studies; I^2=67%)
Monogenic (Leptin/LEPR deficiency)	2	Rare; <1% severe early-onset	Extreme early-onset; hypogonadism; immune dysfunction	Serum leptin; leptin receptor sequencing	Recombinant leptin replacement (dramatic response); glucocorticoid (POMC)	Moderate (1 clinical trial + 1 case series; I^2=0%)
Endocrine Causes	1	<1% of paediatric obesity (cross-sectional data)	Growth deceleration; cushingoid features; TSH elevation	TSH/fT4; 24-h UFC; late-night salivary cortisol; IGF-1	Hormone replacement; endocrine-specific treatment	Low (1 cross-sectional study)

DISCUSSION

4.1 Principal Findings

This systematic review and meta-analysis of 12 primary studies provides, to our knowledge, the first quantitative synthesis of primary data on the secondary causes of childhood obesity. The key findings are as follows: (1) MC4R deficiency accounts for a pooled 3.6% of children with severe early-onset obesity, with comprehensive NGS panels achieving a diagnostic yield of ~9.5%; (2) growth hormone therapy in PWS reduces BMI SDS by 0.82 units (a clinically meaningful effect), with high GRADE certainty supported by one RCT at low risk of bias; (3) hypothalamic obesity develops in 42.5% of children following craniopharyngioma treatment, with substantial heterogeneity; and (4) leptin/leptin-receptor replacement produces dramatic, consistent weight reduction, although the evidence is limited by small sample sizes.

4.2 Contextualisation

Our pooled MC4R prevalence estimate of 3.6% (95% CI, 2.1–5.4%) is consistent with single-center estimates from specialist obesity genetics clinics [35] and population-based NGS registries [41]. The slightly lower pooled estimate relative to some specialist reports reflects the inclusion of broader severity thresholds in the Kleinendorst 2018 cohort (n=1,230), which provides the most rigorous population-based denominator available. The NGS diagnostic yield of ~9.5% from the two cohorts is consistent with emerging evidence from national genomic medicine programs, which report actionable variant rates of 7–12% in carefully phenotyped severe early-onset obesity cohorts.

The high-quality growth hormone evidence (GRADE: High) for PWS stands in marked contrast to the low-certainty evidence for hypothalamic obesity management. This asymmetry reflects both the availability of an RCT for PWS [15] and the inherent difficulty of conducting trials in post-craniopharyngioma populations with severe, treatment-resistant obesity [16]. The absence of any primary RCT data for antipsychotic-induced obesity in children — a particularly common and growing clinical problem — represents a major evidence gap identified by this review.

4.3 Clinical Implications

Clinicians assessing children with obesity should apply a structured red-flag approach (Figure 5) to identify those requiring secondary cause evaluation. The ~10% NGS diagnostic yield in severe early-onset obesity supports genetic testing as a high-value investigation in appropriately phenotyped children, with the potential to identify patients eligible for precision pharmacotherapies, including setmelanotide [31]. Growth hormone therapy should be offered to all eligible children with PWS, supported by high-certainty evidence. For hypothalamic obesity, proactive presurgical hypothalamus-sparing strategies should be discussed given the high post-treatment incidence (42.5%). Management is consistently

multidisciplinary, encompassing endocrinology, clinical genetics, dietetics, and psychology. Pharmacological interventions warrant metabolic monitoring across all secondary cause categories.

4.4 Limitations

Several limitations must be acknowledged. First, the total number of eligible primary studies was small (k=12), reflecting the relative scarcity of primary data on rare secondary obesity subtypes; this limited the number of meta-analyses that could be conducted and widened confidence intervals. Second, significant heterogeneity (I^2=67%) in the hypothalamic obesity prevalence estimate limits the precision of this subgroup. Third, the medication-induced obesity category lacked eligible primary studies (all identified studies were meta-analyses, which were excluded by design), resulting in no primary data synthesis for this clinically important subtype. Fourth, most studies originated from specialist tertiary centers in high-income countries, limiting generalizability to community and lower-resource settings. Fifth, the small sample sizes in the leptin treatment studies (total N=20) preclude robust effect estimates despite the striking I^2=0% and potential for reporting bias in this literature is high. Sixth, endocrine causes were underrepresented in the primary study literature, with only one cross-sectional study providing quantifiable data.

4.5 Future Research Priorities

1. Adequately powered RCTs of antipsychotic-induced weight gain prevention and treatment in children (this review identified no eligible primary trials).
2. Randomized trials of GLP-1 receptor agonists and combination agents for hypothalamic obesity in pediatric populations
3. Title: Population-based NGS prevalence studies in unselected pediatric obesity cohorts to determine real-world diagnostic yield
4. Long-term RCT follow-up data for setmelanotide in pediatric MC4R/POMC/LEPR-deficient patients
5. Community-based epidemiological studies in low-and middle-income countries to assess the generalizability of secondary obesity prevalence estimates
6. Development and prospective validation of clinical screening algorithms to guide cost-effective secondary obesity evaluation
7. Natural history cohort studies for recently identified monogenic variants beyond MC4R and leptin pathway genes.

CONCLUSIONS

This systematic review and meta-analysis of 12 primary studies provides the first quantitative, primary-data-based synthesis of the secondary causes of childhood obesity. Growth hormone therapy in Prader-Willi syndrome achieves a clinically meaningful and statistically robust reduction in body mass index (BMI) SDS (MD −0.82; GRADE: High). Comprehensive genetic testing yields a diagnosis in approximately 1 in 10 children with severe early-onset obesity, supporting routine next-generation sequencing (NGS) evaluation in appropriately phenotyped patients. Hypothalamic obesity develops in over 40% of children following craniopharyngioma treatment and remains highly treatment-resistant, highlighting the need for prevention-focused surgical strategies and future pharmacological trials. Targeted leptin replacement produces dramatic weight loss in congenital leptin/LEPR-deficient children. A structured red-flag clinical algorithm guides cost-effective evaluation. Future primary research, particularly randomized controlled trials (RCTs) for medication-induced and hypothalamic obesity subtypes, is urgently required to address the substantial evidence gaps identified by this review.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization: M.A., A.S.; methodology: M.A., A.S., B.A.; formal analysis and meta-analysis: M.A., A.S.; data curation and extraction: all authors; writing – original draft: M.A., A.S.; writing – review and editing: all authors; supervision: A.A.S. All authors have approved the final version.

Ethical Approval

Not applicable (systematic review and meta-analysis of published primary literature).

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