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Meta-analyses

Feasibility, safety, and efficacy of dietary or lifestyle interventions for hypothalamic obesity: A systematic review

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SUMMARY

Background & aims: A dysfunctional hypothalamus may result in decreased feelings of satiety (hyperphagia), decreased energy expenditure, and increased fat storage as a consequence of hyperinsulinemia. Hypothalamic dysfunction may thus lead to morbid obesity and can be encountered in childhood as a consequence of congenital, genetic, or acquired disorders. There is currently no effective treatment for hypothalamic obesity (HO). However, comparable to alimentary obesity, dietary and lifestyle interventions may be considered the cornerstones of obesity treatment. We questioned the effect of dietary or lifestyle interventions for HO and systematically searched the literature for evidence on feasibility, safety, or efficacy of dietary or lifestyle interventions for childhood hypothalamic overweight or obesity.
Methods: A systematic search was conducted in MEDLINE (including Cochrane Library), EMBASE, and CINAHL (May 2023). Studies assessing feasibility, safety, or efficacy of any dietary or lifestyle intervention in children with hypothalamic overweight or obesity, were included. Animal studies, studies on non-diet interventions, and studies with no full text available were excluded. Because the number of studies to be included was low, the search was repeated for adults with hypothalamic overweight or obesity. Risk of bias was assessed with an adapted Cochrane Risk of Bias Tool. Level of evidence was assessed using the GRADE system. Descriptive data were described, as pooled-data analysis was not possible due to heterogeneity of included studies.
Results: In total, twelve studies were included, with a total number of 118 patients (age 1–19 years) of whom one with craniopharyngioma, one with ROHHAD-NET syndrome, 50 with monogenic obesity, and 66 with Prader–Willi syndrome (PWS). Four studies reported a dietary intervention as feasible. However, parents did experience difficulties with children still stealing food, and especially lowering carbohydrates was considered to be challenging. Seven studies reported on efficacy of a dietary intervention: a well-balanced restrictive caloric diet (30% fat, 45% carbohydrates, and 25% protein) and various hypocaloric diets (8–10 kcal/cm/day) were considered effective in terms of weight stabilization or decrease. No negative effect on linear growth was reported. Four studies reported on specific lifestyle interventions, of which three also included a dietary intervention. Combined dietary and lifestyle intervention resulted in decreased BMI, although BMI returned to baseline values on long-term. One additional study was

Abbreviations: AgRP, agouti- related protein; α-MSH, alpha-Melanocyte-stimulating hormone; ARC, arcuate nucleus; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CART, cocaine-amphetamine-related transcript; CLIP, corticotropin-like-intermediate lobe peptide; CRH, corticotropin releasing hormone; DMV, dorsal motor nucleus of the vagus; HD, hypothalamic dysfunction; HO, hypothalamic obesity; LC, locus coeruleus; LHA, lateral hypothalamic area; MCH, melanin concentrating hormone; MC3R/MC4R, melanocortion-3/4- receptor; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PWS, Prader Willi syndrome; REE, resting energy expenditure; ROHHAD-NET, rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome; VMH, ventromedial hypothalamus.

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identified in adults after brain trauma and showed a significant reduction in BMI in one out of eight patients after a combined dietary and lifestyle intervention.
Conclusions: Hypocaloric diet or restrictive macronutrient diet with lower percentage of carbohydrates seems feasible and effective for childhood HO, although most of the studies had a high risk of bias, small cohorts without control groups, and were conducted in children with PWS only, compromising the generalizability. Lifestyle interventions only resulted in BMI decrease in short-term, indicating that additional guidance is needed to sustain its effect in the long-term. Literature on feasibility and efficacy of a dietary or lifestyle intervention for hypothalamic overweight or obesity is scarce, especially in children with acquired HO (following treatment for a suprasellar tumor). There is need for prospective (controlled) studies to determine which dietary and lifestyle intervention are most helpful for this specific patient group.

1. Introduction

The hypothalamus is an endocrine organ, located in the center of the brain, and is the key regulator of the body homeostasis. Hypothalamic dysfunction (HD) can result in hypothalamic overweight or obesity. One of the main functions of the hypothalamus is regulation of satiety and resting energy expenditure (REE) [1,2]. Inadequate function of the hypothalamus may result, amongst other symptoms, in hyperphagia, which together with a low REE results in weight gain, aggravating into morbid obesity [3]. However, not all patients with HD experience hyperphagia. Overweight and obesity may also be the result of an diminished expenditure (in terms of physical activity together with REE) in combination with increased fat storage as a consequence of increased insulin secretion by damage to efferent hypothalamic pathways resulting in an increased tone of the parasympathetic system [4] (See Fig. 1). Furthermore, next to the aforementioned hyperphagia, low REE and increased insulin production, also behavioral control can be impaired in patients with HD, resulting in craving, hoarding, and loss of initiative. Due to loss of initiative, these children often experience difficulties with reaching targets for a healthy lifestyle. Lastly, also in children with congenital (e.g. septo-optic dysplasia) or acquired dysfunction (e.g. craniopharyngioma) visual impairment may be present, contributing to a lower ability to reach the advised duration of exercise per day [5]. Physical activity and fitness are impaired in children with craniopharyngioma [6] (See Fig. 2).

HD may thus lead to hypothalamic overweight or obesity. HD may be congenital, genetic, or acquired. Examples of congenital causes are syndromic obesity such as Prader–Willi syndrome (PWS) or rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor (ROHHAD-NET) syndrome [8]. Examples of genetic causes are monogenic obesity such as leptin deficiency or melanocortin 4 receptor (MC4R) deficiency [9,10]. Acquired HD can be seen in children with suprasellar brain tumors, such as craniopharyngioma, that may develop hypothalamic obesity (HO) due to brain trauma (the tumor itself, or aggravation due to neurosurgical intervention and/or radiotherapy) [11]. Hypothalamic overweight or obesity is defined as overweight/obesity (according to national guidelines or WHO standards), accompanied by rapid weight gain and other symptoms of HD. Although there are many differences between congenital and acquired causes of HO, striking similarities are found with regards to the development of HO over time, for example: young children with a suprasellar low-grade glioma may present with diencephalic syndrome, characterized by failure to thrive [12], which develops into HO during the course of disease [13]. Similarly, children with PWS present with feeding problems and underweight at young age, followed by weight gain and hyperphagia at approximately the age of four years [14].

HO may have severe consequences later in life, such as cardiovascular, metabolic (diabetes mellitus type 2), respiratory (OSAS) but also psychologic (depression) and increased early mortality [15–17].

Management of HO is challenging and so far, weight gain has been refractory to various treatments in most patients, both short-term (weeks) and long-term (nine years). An individualized approach for treatment of HO is encouraged [5]. By characterizing patients, some interventions may be partially effective, but for most patients, HO remains an untreatable disease [10,18]. Currently there are ongoing trials investigating drugs targeting satiety and energy expenditure in HO, and even more rigorous treatments, such as bariatric surgery, are considered treatment options for children with HO [19–21]. Still, similar to “alimentary” obesity, diet and lifestyle remain the cornerstone of hypothalamic obesity treatment [5]. In our clinical practice, we encountered several very positive experiences on body mass index (BMI) of children with HO with dietary and lifestyle intervention encouraged by parents, without other additional pharmacologic treatment (Fig. 3).

However, because HD leads to specific disruptions of energy balance and behavior of the patients, it may be questioned whether dietary and lifestyle recommendations now used for alimentary obesity are also most appropriate for children with HO. For example, due to damage to efferent pathways and the parasympathetic nerve system, fat storage is increased. This may be an argument to limit carbohydrate intake.

We questioned the state of existing evidence on feasibility, safety, and efficacy of dietary and/or lifestyle interventions for HO in childhood. Such evidence may form the basis for implementations of diets and lifestyle programs for HO in the clinic but also for future studies on optimizing pharmacological interventions in patients with HO. If diet and lifestyle can be further optimized in patients with HO, this may have a synergistic effect and enhance the effects of new pharmacological treatments.

2. Material & methods

2.1. Search strategy

MEDLINE (including Cochrane Library), EMBASE, and CINAHL were searched for published literature using search terms for childhood hypothalamic overweight or obesity and dietary or lifestyle intervention (Supplement 1 includes full search terms). The search was conducted in May, 2023. Duplicates were removed using Endnote (X9.3, United States). Both title/abstract screening and full text screening was performed by two groups of two independent reviewers (IvR & BR, MvdB & JD) using Rayyan [22]. Conflicts were resolved through discussion with four of the reviewers (IvR, BR, MvdB, JD). In order to identify relevant manuscripts that were

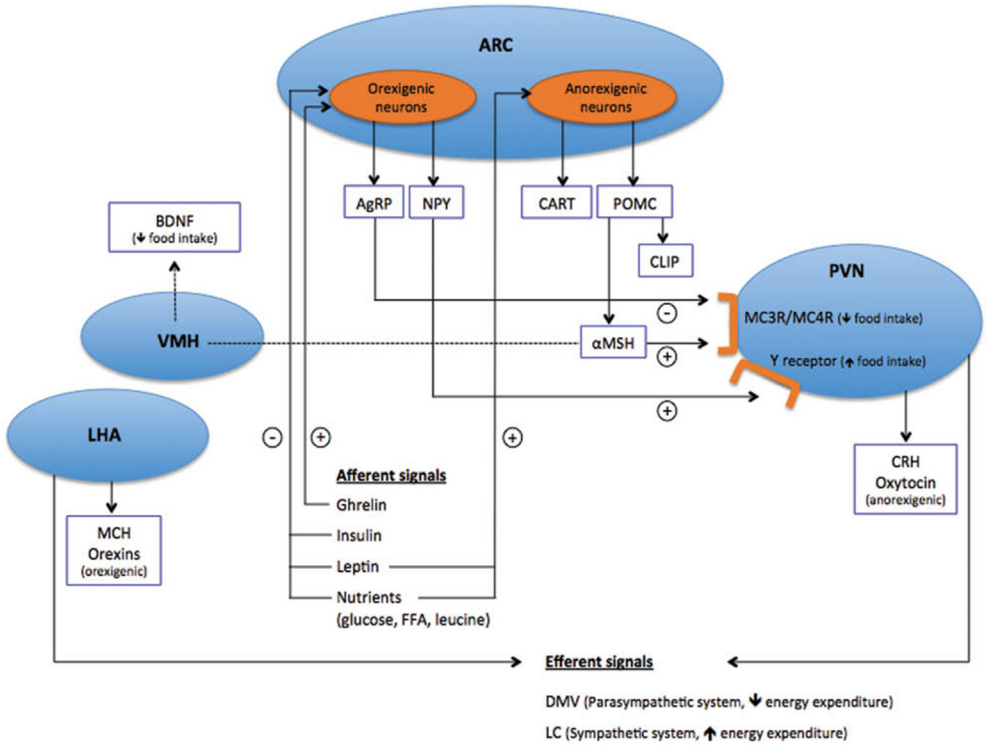


Fig. 1. Scheme of pathways involved in energy balance regulated by the hypothalamus. Published with permission from authors and publisher (Haliloglu et al., 2015) [7].AgRP = agouti- = related protein, α-MSH = alpha-Melanocyte-stimulating hormone, ARC = arcuate nucleus, BDNF = brain-derived neurotrophic factor, CART = cocaine-amphetamine-related transcript, CLIP = corticotropin-like-intermediate lobe peptide, CRH = corticotropin releasing hormone, DMV = dorsal motor nucleus of the vagus, LC = locus coeruleus, LHA = lateral hypothalamic area, MCH = melanin concentrating hormone, MC3R/MC4R = melanocortion-3/4- receptor, NPY = neuropeptide Y, POMC = proopiomelanocortin, PVN = paraventricular nucleus, VMH = ventromedial hypothalamus.

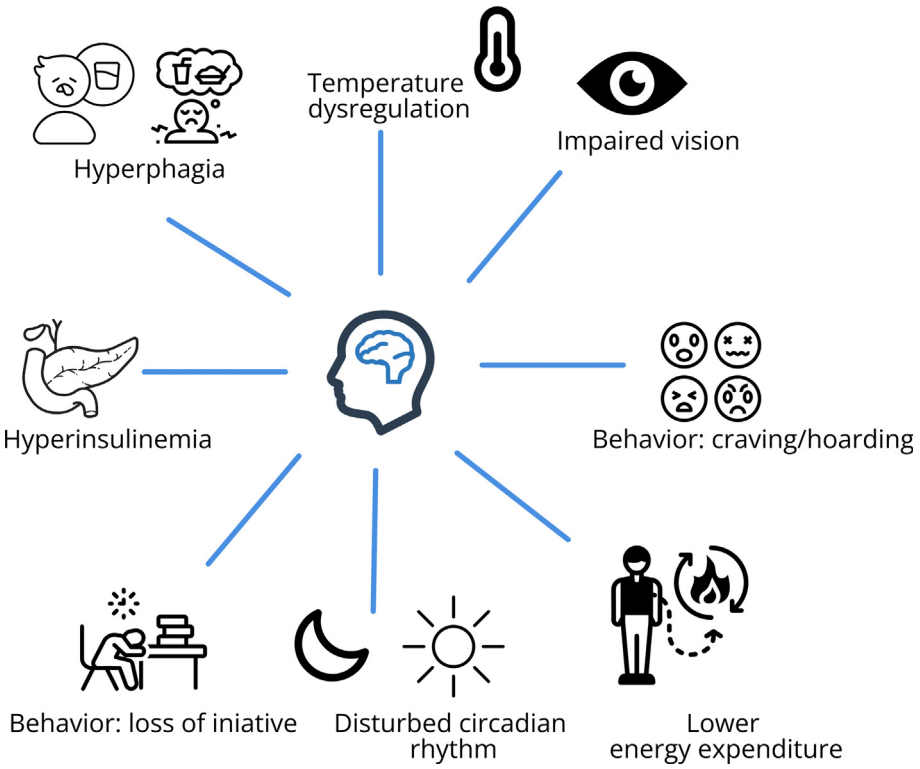


Fig. 2. (examples of) Clinical signs and symptoms that may be encountered in patients with acquired hypothalamic dysfunction and contribute to hypothalamic overweight/obesity.

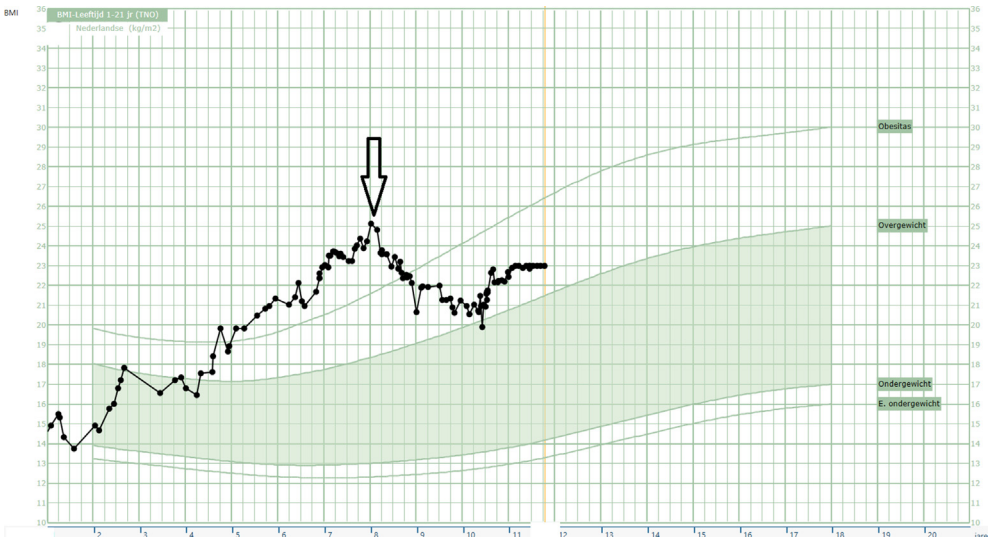


Fig. 3. Example of a BMI growth curve of a girl after diet/lifestyle intervention for HO. Intervention included caloric restriction of 600 kcal/day (with a resting energy expenditure of 1050 kcal) and 30 min on a home trainer daily. Arrow indicates start of diet/lifestyle intervention.

not included in the search, snowballing was performed by all reviewers, meaning that all references of the included manuscripts were checked for relevance.

2.2. Eligibility criteria

Manuscripts were included if they fulfilled the following criteria; reporting on dietary or lifestyle interventions (without pharmacotherapy) for children or adolescents with hypothalamic overweight or obesity of any cause, describing feasibility, safety, or efficacy (outcome on body weight or BMI). Exclusion criteria were: animal studies, no full text available, studies with a non-diet intervention and studies only reporting on adults above 21 years of age. Studies not specifying type or duration of diet were excluded. Randomized controlled trials, prospective clinical trials, as well as retrospective studies and case reports were included. Reviews were not included.

As identified literature in children was scarce, a second search was performed, also including adults. This was done by leaving out search terms on childhood. All articles were again screened independently by all reviewers. Results of this search are reported separately in this manuscript.

2.3. Outcome

Primary outcomes included in this review were feasibility, safety, or efficacy of a dietary or lifestyle intervention for hypothalamic overweight or obesity. Other parameters that were searched for and collected in manuscripts were: study type, population and number of patients, group definition of both case and control group, age, and biological sex of patients.

2.4. Critical appraisal

After full text screening, included articles were assessed on validity and applicability. Consensus on scoring criteria was reached beforehand. Applicability was scored by using a predefined applicability scoring system in accordance with the research question (Supplement 2).

2.5. Data analysis

The PRISMA flow diagram and PRISMA checklist were used for data reporting [23]. Data was collected from manuscripts by two reviewers independently (IvR & MvdB). For all studies, the effect of dietary or lifestyle intervention used was displayed as mean difference in weight, or BMI, or BMI SDS reduction. For Risk of Bias assessment, the Cochrane Risk of Bias Tool was adapted to observational studies, similarly to the International Guideline Harmonization group [24,25]. Level of evidence was determined by using the GRADE system [26]. Due to heterogeneity between studies, pooled analysis was not performed.

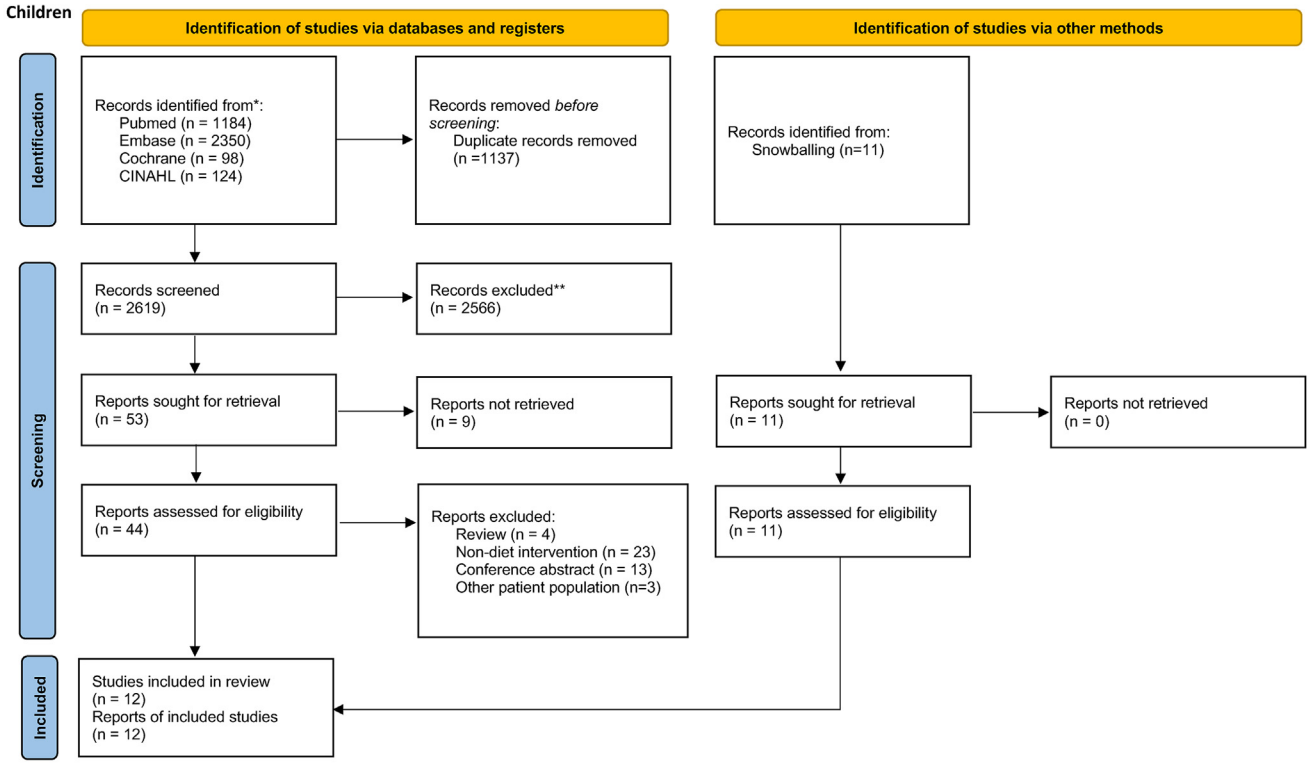
3. Results

After deduplication, 2619 articles were eligible for title/abstract screening (Fig. 4). After full text screening, one original article fulfilled inclusion criteria of the search [27], and six reviews were identified [28–33]. Of these six reviews, the original articles matching our inclusion criteria were included after snowballing (n = 6) [34–39], and further snowballing resulted in five additional articles [40–44]. In total twelve articles were included. In Supplement 3 for each study it is shown in which review it was identified.

Baseline characteristics of included studies are displayed in Table 1. All but two of the studies scored high on applicability criteria, one scored moderate, and one scored low (Table 2). Summary of the results are shown in Table 3 and Table 4.

3.1. Feasibility of dietary or lifestyle intervention

In total, four studies reported on feasibility of a dietary intervention. Although it was not systematically examined, a study on a well-balanced restrictive caloric diet reported that non-compliance was most often related to difficulties with lowering carbohydrate intake. Patients reported that decreasing fat intake was easier than decreasing carbohydrates in the diet [34]. In the feasibility study for a Modified Atkins Diet, two patients out of seven were not able to comply. One reported that the diet was not feasible because lunch at school did not correspond well with the diet. Furthermore, in



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

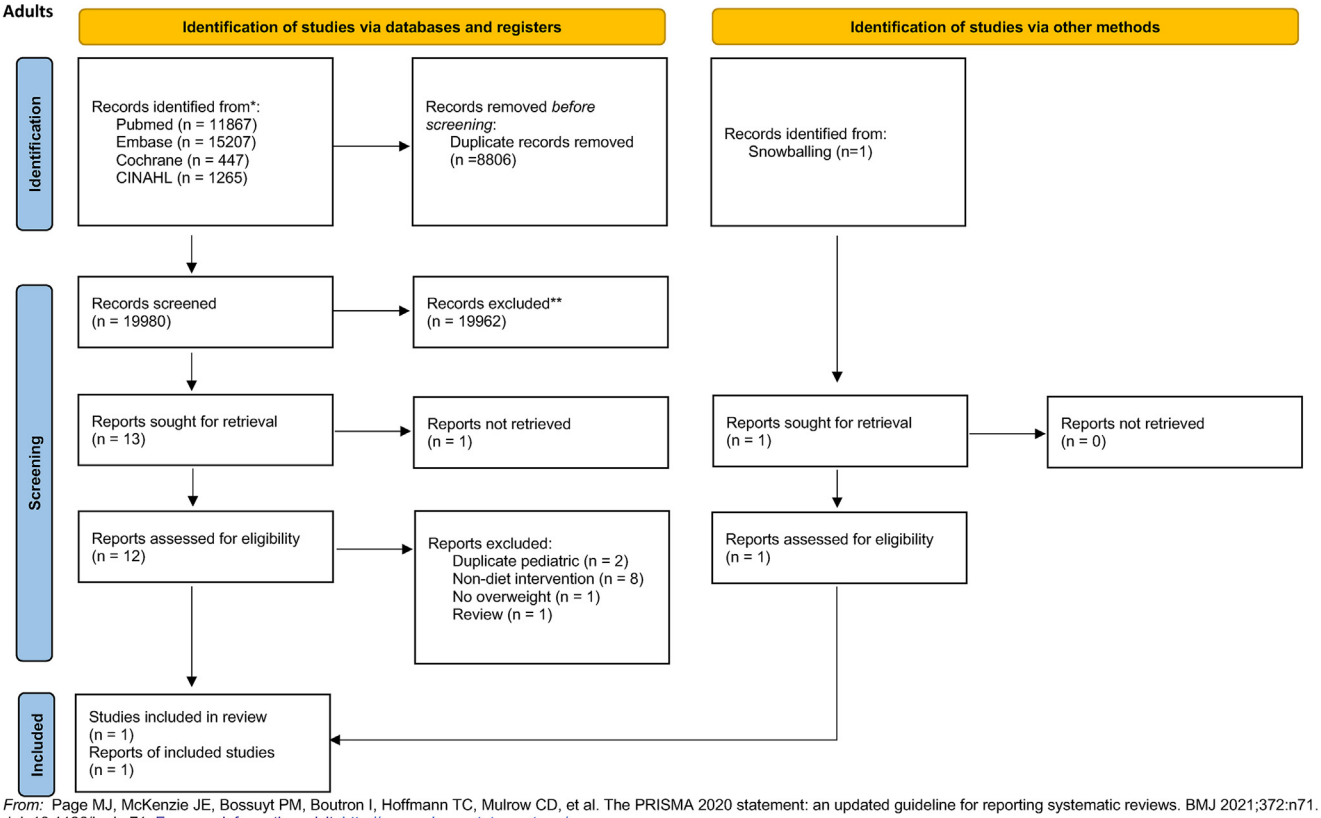


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Fig. 4. PRISMA flow diagram.

Table 1
Baseline characteristics of included studies.

Reference	Subjects (n) and diagnosis	Age (y)	Study design	Dietary/lifestyle intervention	Duration	Method of evaluation of diet or lifestyle	Evaluation of anthropometrics
[34] Miller et al., 2013	Prader–Willi syndrome (n = 63), n = 33 in the intervention group	2–10	Intervention, as part of prospective longitudinal cohort study	Energy restricted diet with well-balanced macronutrient composition (30% fat, 45% carbohydrates, 25% protein, >20 g fiber); feedback of dietitian after receiving dietary records	Follow-up 5–7 years; yearly study measurements if child was aged <4 years and every other year if child was aged >4 years	3-day diet history analysis including at least one school day and one weekend day (every 6 months) from patient and sibling; questionnaire about food behavior (each visit)	Height, weight, BMI Z-score
[35] Felix et al., 2020	Prader–Willi syndrome (n = 7)	6–12	Clinical feasibility study	Modified Atkins diet (10 –15 g net carbohydrate limit, pediatric multivitamin, vitamin D and calcium supplement, protein/fat on individual basis)	12 months (initial teaching, 4 months on diet, 4 months off diet); 3 study measurements	Questionnaires regarding hyperphagia	Height, weight, BMI, BMI Z-score
[42] Bonfig et, 2009	Prader–Willi syndrome (n = 5)	14–19	Intervention without control group	Strict fat-reduced, and carbohydrate-modified diet (10 kcal/cm/day; 25% protein, 20% fat, 55% modified carbohydrates)	5-year diet period; study measurements every 6–12 months	Questionnaire regarding hyperphagic phases and food-craving behavior	Height, weight, BMI SDS, weight-for-height index
[36] Lima et al., 2016	Prader–Willi syndrome (n = 5)	6–16	Intervention without control group	Hypocaloric diet (10 kcal/cm/day, starting with 14 kcal/cm/day for maintenance and 7 kcal/cm/day for weight loss; grains 150 kcal; vegetables 15 kcal; fruits 35 kcal; legumes 55 kcal; meat/eggs190 kcal; dairy 120 kcal)	8 months; 10 sessions, 2 anthropometric measures (pre- and post intervention)	NA	Height, weight, BMI
[37] Irizarry et al., 2019	Prader–Willi syndrome (n = 8), but only n = 2 patients had a BMI SDS >2.0, the other children had normal weight	9–18	Intervention with cross-over design	Two diets: carbohydrate restriction and fat restriction (low carb: 15% carb, 65% fat, 20% protein vs low fat: 65% carb, 15% fat, 20% protein; 80% of EER ((estimated energy requirement) according to age/gender; daily multivitamin)	Diets were only consumed during 2 hospital admissions of 72 h; consume either low carb or low fat diet and 4 weeks later the other diet	Questionnaire regarding pre-prandial hunger and post-prandial satiety	Height, weight, BMI, BMI SDS
[43] Holm et al., 1976	Prader–Willi syndrome (n = 14)	1–18	Intervention without control group	Weight control program (8 –9 kcal/cm/day; 15–20% protein, remaining fat and carbohydrates)	Follow-up 10 months –6 years and 7 months (mean: 2 years and 10 months)	7-day food diary (every 3 months)	Height, weight
[38] Lee et al., 1992	Craniopharyngioma (n = 1)	14	Case report	Protein-sparing modified fast (567 kcal/day, 71g protein, 27g fat, 10g carbohydrates; daily supplementation vitamins and minerals)	Introduction of PSMF diet during hospital admission of 7 days, which was continued for 9 months. Afterwards, maintenance diet (1500 kcal/day) for 12 months	NA	Weight

(*continued on next page*)

Table 1 (*continued*)

Reference	Subjects (n) and diagnosis	Age (y)	Study design	Dietary/lifestyle intervention	Duration	Method of evaluation of diet or lifestyle	Evaluation of anthropometrics
[27] Marpuri et al., 2022	ROHHAD-NET syndrome (n = 1)	6	Case report	Caloric restriction (≤1000 calories/day) and macronutrient plan of ≤100 g carbohydrates daily	Six months	NA	Height, weight, BMI
[39] Reinehr et al., 2009	MC4 receptor mutation (n = 16)	5–16	Intervention trial in 2 groups with obesity: with mutation (hypothalamic obesity) and without mutation (control group, "general" obesity)	1-year lifestyle intervention including parents course, behavior therapy, talk rounds, nutritional course, individual psychological therapy, exercise therapy. Nutritional course on 'optimized mixed diet' (30% fat, 15% proteins, 55% carbohydrates) + 'traffic-light system'	1 year	Three-day weighed dietary records	BMI SDS
[40] Hainerová et al., 2007	MC4 receptor mutation (n = 4)	13–17	Intervention trial in 2 groups with obesity: with mutation (hypothalamic obesity) and without mutation (control group, "general" obesity)	6-week lifestyle program including: physical exercise of 4 h/day, energy-restricted diet (fat ≤30%, carbohydrates 50–55%, total energy 5–7 MJ/day) + education and psychologic support, while being in an inpatient clinic	6 weeks	NA	BMI Z score
[41] Trier et al., 2021	MC4 receptor mutation (n = 24)	2–19	Intervention trial in 2 groups with obesity: with mutation (hypothalamic obesity) and without mutation (control group, "general" obesity)	Low intensity individual lifestyle program including eating behavior, physical activity, sources and amount of nutrition, psychosocial functioning, sleep pattern	6 months–4 years	NA	Height, weight, BMI, BMI SDS, height-for-age SDS
[44] Morell-Azanza et al., 2019	MC4 receptor mutation (n = 7)	8–14	Randomized controlled trial	1-year lifestyle intervention including a hypocaloric Mediterranean diet + exercise of 200 min/week	8-week intensive program and 10 months of follow-up	NA	Weight, height, body fat, BMI, BMI SDS,

Table 2
Applicability criteria.

	Domain	Determinant	Outcome	Applicability
(34) Miller et al, 2013	+	+	+	+
(35) Felix et al, 2020	+	+	+	+
(42) Bonfig et, 2009	+	+	+	+
(36) Lima et al, 2016	+	+	+	+
(37) Irizarry et al, 2019	~	~	~	~
(43) Holm et al, 1976	+	+	+	+
(38) Lee et al, 1992	+	+	~	+
(27) Marpuri et al, 2022	+	+	~	+
(39) Reinehr et al, 2009	+	+	+	+
(40) Hainerová et al , 2007	+	+	~	+
(41) Trier et al, 2021	+	-	~	-
(44) Morell-Azanza et al, 2019	+	+	~	+

Legend

-	Low	~	Moderate	+	High

both children there were factors in the household that made it difficult to comply (stress, siblings not willing to adapt, financial costs). For the other four participants, parents indicated that the diet was feasible. Overall feasibility of a Modified Atkins diet was clear from the fact that all these participants (n = 5) continued the intervention even after the "off-diet" period [35]. In the study on a hypocaloric diet with 10 kcal/cm/day, parents faced difficulties with keeping their child to the diet because of hyperphagic behavior but all of them eventually succeeded [36]. In a study on a hypocaloric diet of 8–9 kcal/cm/day, maintenance of hyperphagic behavior was observed in 11 out of 14 children, reflected in still stealing food during the intervention, thereby not complying to the intervention [43]. One study reported on feasibility of a lifestyle intervention. For this study, participants had to complete a motivation phase of eight weeks, in which they were required to join exercise groups. Of 16 children with MC4R mutation (hypothalamic obesity), 56% did not complete the motivation phase, this was similar to the group without mutation ("general" obesity) (48%). One additional child dropped out of the study during the intervention period [39].

3.2. Safety of intervention

In total, six studies reported on side-effects of the diet assessed. Four studies showed that the diet assessed did not result in growth retardation in terms of height [35,36,38,43]. Three studies reported on safety in terms of laboratory investigations. Two studies showed no aberrant lab results [35,42]. In one study, a carbohydrate-restricted diet resulted in higher inflammatory markers and elevated AST and ALT, possibly reflecting liver steatosis [37]. No studies reported on side-effects of lifestyle interventions.

3.3. Effect on body weight

In total, seven out of 12 studies reported on the effect of a dietary intervention on body weight or BMI. In total, four out of 12 studies specifically reported on the effect of lifestyle interventions on BMI (three also including a dietary intervention).

In one study including 63 patients, a well-balanced restrictive caloric diet (defined as 30% fat, 45% carbohydrates and 25% protein, with a goal of at least 20 g of fiber per day) was found to be effective in BMI reduction [34]. In comparison to a "normal diet" (approximated 10–23% fat, 50–70% carbohydrates and 15–20% protein, with 12 g or less of fiber per day) BMI SDS after intervention was 0.3 for the intervention group and 2.3 SDS for the control group ($P < 0.001$) after a follow-up of minimum five years and maximum seven years. In both groups caloric intake had been restricted to the individual REE measured [34]. In a study including seven patients, the Modified Atkins Diet resulted in a BMI decrease in four out of five participants (two patients were excluded because of non-compliance) with an average decrease in BMI of 0.2 SDS after a follow-up time of one year [35].

In two studies, a hypocaloric diet of 10 kcal/cm/day resulted in a reduction of BMI [36,42], and in one of the studies the intervention and its effect was maintained for a period of six years [42]. In a study on low fat and low carbohydrate diet, there was no specific examination of body weight and it was only stated that weight did not significantly change but there was no individual information on patients with obesity in this study [37]. In a weight control program with 8–9 kcal/cm/day and 15–20% protein, 11 out of 12 children lost weight and eight of them remained stable weight with the diet over a period up to five years [43]. A protein-sparing modified fast diet in a boy with craniopharyngioma resulted in weight loss of almost 40 kg (from 109 kg to 71 kg, BMI was not mentioned) [38]. In a case of a patient with ROHHAD-NET syndrome, a caloric restriction of less than 1000 calories a day (in a six-year old) combined with a macronutrient plan of less than 100 g carbohydrates a day did not result in weight loss (BMI increased with 0.1 SD) [27].

In two trials on a lifestyle intervention (including a dietary intervention) for children with MC4R mutation, there was a significant reduction in BMI; mean BMI decreased −0.35 SDS, and −0.95 kg/m2, respectively [39,40]. However, in the trial with a lifestyle intervention for one year, there was only a decrease in BMI SDS during the first year, while two years after baseline BMI returned to baseline values in the group with MC4R mutation, whereas there was a decrease in BMI SDS in the group without mutation [39]. In another trial on a low-intensity individualized lifestyle intervention for MC4R mutation, there was no significant decrease in BMI SDS, but BMI did stabilize (mean difference BMI SDS -0.033) [41]. In a randomized controlled trial on an intensive lifestyle program (consisting of 200 min exercise per week) including a dietary intervention (hypocaloric Mediterranean diet), after eight weeks, five out of seven children in the intervention group achieved significant reduction in BMI SDS compared to baseline (mean difference in BMI SDS -0.74), whereas the decrease of BMI SDS was not significant in the usual care group. However,

Table 3
Summary of results on body weight.

Reference	Subjects and diagnosis (n)	Age (y)	Study design	Dietary/lifestyle intervention	Outcome on body weight
[34] Miller et al., 2013	Prader–Willi syndrome (n = 63), n = 33 in the intervention group	2–10	Intervention, as part of prospective longitudinal cohort study	Energy restricted diet with well-balanced macronutrient composition (30% fat, 45% carbohydrates, 25% protein, >20 g fiber); feedback of dietitian after receiving dietary records	Compliant children had lower body fat percentage (19.8% versus 41.9%, P < 0.001), lower BMI SD score (0.3 SDS vs 2.3 SDS, P < 0.001)
[35] Felix et al., 2020	Prader–Willi syndrome (n = 7)	6–12	Clinical feasibility study	Modified Atkins diet (10–15 g net carbohydrate limit, pediatric multivitamin, vitamin D and calcium supplement, protein/fat on individual basis)	No significant weight loss, except for one child (−2.9 kg) BMI z-scores improved (3 out of 4), average decrease of −0.21 SD
[42] Bonfig et, 2009	Prader–Willi syndrome (n = 5)	14–19	Intervention without control group	Strict fat-reduced, and carbohydrate-modified diet (10 kcal/cm/day; 25% protein, 20% fat, 55% modified carbohydrates)	BMI, BMI SDS, and weight-for-height index dropped significantly after 1 year, 2 years, and after 4–6 years
[36] Lima et al., 2016	Prader–Willi syndrome (n = 5)	6–16	Intervention without control group	Hypocaloric diet (10 kcal/cm/day, starting with 14 kcal/cm/day for maintenance and 7 kcal/cm/day for weight loss; grains 150 kcal; vegetables 15 kcal; fruits 35 kcal; legumes 55 kcal; meat/eggs190 kcal; dairy 120 kcal)	Body weight did not significantly change (mean −1.44 kg), but height (increased) and BMI (decreased) did. Mean BMI was 37.03 pre-intervention and 25.71 post-intervention (p = 0.04)
[37] Irizarry et al., 2019	Prader–Willi syndrome (n = 8), but only n = 2 patients had a BMI SDS >2.0, the other children were normal weight	9–18	Intervention with cross-over design	Two diets: carbohydrate restriction and fat restriction during a 72h hospital admission (low carb: 15% carb, 65% fat, 20% protein vs low fat: 65% carb, 15% fat, 20% protein; 80% of EER according to age/gender; daily multivitamin)	Effect of low carb and low fat diet on anthropometrics and body composition not investigated. Only stated that there was "no significant effect on weight" (p = 0.46)
[43] Holm et al., 1976	Prader–Willi syndrome (n = 14)	1–18	Intervention without control group	Weight control program (8–9 kcal/cm/day; 15–20% protein, remaining fat and carbohydrates)	11 children lost weight. After weight loss, 8 children maintained their weight over time (range: 6 months–5 years)
[38] Lee et al., 1992	Craniopharyngioma (n = 1)	14	Case report	Protein-sparing modified fast (567 kcal/day, 71g protein, 27g fat, 10g carbohydrates; daily supplementation vitamins and minerals)	Weight decreased to 71 kg (from 109 kg) after 9 months of PSMF treatment
[27] Marpuri et al., 2022	ROHHAD-NET syndrome (n = 1)	6	Case report	Caloric restriction (≤1000 calories/day) and macronutrient plan of ≤100 g carbohydrates daily	Weight increased with 6 kg and height increased with 4 cm in 6 months. BMI Z score increased by 0.13 SD and percentage BMI above p > 95 increased by 2% in 6 months
[39] Reinehr et al., 2009	MC4 receptor mutation (n = 16)	5–16	Intervention trial in 2 groups with obesity: with mutation and without mutation (control group)	1-year lifestyle intervention including parents course, behavior therapy, nutritional course, individual psychological family therapy, exercise therapy. Nutritional course on 'optimized mixed diet' (30% fat, 15% proteins, 55% carbohydrates) + 'traffic-light system'	After 1 year there was a significant reduction in BMI SDS (mean −0.35) similar to the control group. After 2 years there was no decrease in BMI SDS compared to baseline in the MC4R mutation group, whereas there was a decrease of BMI SDS in the control group (P < 0.001)
[40] Hainerová et al., 2007	MC4 receptor mutation (n = 4)	13–17	Intervention trial in 2 groups with obesity: with mutation and without mutation (control group)	6-week lifestyle program including: physical exercise of 4 h/day, energy-restricted diet (fat ≤30%, carbohydrates 50–55%, total energy 5–7 MJ/day) + education and psychologic support	After 6 weeks there was a reduction in BMI of mean 0.95 kg/m2 similar to the control group
[41] Trier et al., 2021	MC4 receptor mutation (n = 24)	2–19	Intervention trial in 2 groups with obesity: with mutation and without mutation (control group)	Low intensity individual lifestyle program including eating behavior, physical activity, sources and amount of nutrition, psychosocial functioning, sleep pattern	There was no significant decrease in BMI SDS in the mutation group. However there was stabilization of BMI (mean difference −0.033 SDS) There was a decrease in BMI SDS in the control group

Table 3 (*continued*)

Reference	Subjects and diagnosis (n)	Age (y)	Study design	Dietary/lifestyle intervention	Outcome on body weight
[44] Morell-Azanza et al., 2019	MC4 receptor mutation (n = 7)	8–14	Randomized controlled trial	1-year lifestyle intervention including a hypocaloric Mediterranean diet + exercise of 200 min/week	After 8 weeks there was a significant reduction of BMI SDS compared to baseline in 5 of the 8 patients (mean decrease −0.74 SDS) compared to none of the patients in the control group. After 1 year, there was no significant reduction in BMI compared to baseline in the intervention group, however 4 out of 6 patients had a decrease in BMI (mean −1.0 and −0.8 depending on the type of mutation)

after one year, there was no significant decrease in BMI SDS observed in both groups [44].

3.4. Adults

The search in adults revealed one additional study (*Supplement 4*). In a randomized trial on pharmacotherapy for adults with hypothalamic obesity, the intervention group received pharmacotherapy in addition to a lifestyle intervention and the control group received a lifestyle intervention only, consisting of a hypocaloric diet (30% total energy from fat, 20% protein, and 50% carbohydrates, and a total negative balance of minus 300 kcal per day), monthly advice from a dietitian, and physical activity for more than 30 min. a day [45]. Eight patients were included in the control group (lifestyle intervention only). No safety events were observed. One out of eight patients had a weight loss of more than 5%. Mean weight loss was −0.3% for all patients (range −4.3% to +3.6%) [45].

3.5. Risk of bias and level of evidence

Results of the GRADE-scoring are included in *Supplement 5*. All but one of the studies were scored as having a high risk of bias as there was no randomization in the studies or a proper control group. One of the lifestyle intervention studies (including a dietary intervention) was a randomized controlled trial. This study was scored as medium risk of bias with moderate quality of evidence. Three studies included a control group of children with general obesity but there was no placebo or non-intervention.

4. Discussion

Hypothalamic overweight or obesity in childhood can be a major problem and although new pharmacotherapeutic approaches are being developed [18,46], dietary and lifestyle interventions will remain the cornerstone of management. HO is not a new phenomenon, especially in children with monogenetic disease or craniopharyngioma, so it is surprising to find so little evidence on which diet to recommend to children with HO. In this systematic review, only twelve, low-to-medium level evidence studies could be identified. Hypocaloric and well-balanced restrictive macronutrient diets seem feasible and might result in weight stabilization (considered an achievement in patients with HO) or even weight loss. These results emphasize the need for future studies addressing the question which diet or lifestyle intervention would best benefit this specific patient group to help them conquer the detrimental effects of obesity.

4.1. Feasibility of dietary or lifestyle interventions

In children with alimentary obesity there are high levels of non-compliance to weight programs, increasing up to 50% [47]. Children with HO can additionally experience severe hyperphagia, although this may differ greatly between patients and may even be present in children with alimentary obesity. Also, specifically in children with HO, behavioral problems can be present with hoarding, rage, and obsessive behavior [48,49]. This may greatly influence feasibility of any proposed intervention. In the studies, some parents stated that lowering carbohydrates was less feasible than lowering fat. Reasons to not comply to the diet included difficulties in adaptations in the household or at school, personal stressors, and financial costs. The fact that almost half of the children (47%) dropped out during the motivation phase in a lifestyle intervention study including children with MC4R mutation, suggests that such programs will only be feasible for a selective group of children [39]. There were no specific physical safety concerns nor any observed effects on longitudinal growth after implementing a hypocaloric diet.

4.2. Efficacy of dietary or lifestyle interventions

Most of the studies identified were dietary interventions without a control group in children with PWS. In five (low quality) studies, we found a hypocaloric diet of 8–10 kcal/cm/day, the Modified Atkins diet, and a well-balanced restrictive macronutrient diet (defined as 30% fat, 45% carbohydrates, and 25% protein) to result in weight loss [34–36,42,43]. A protein-sparing modified fast diet resulted in weight loss in a child with craniopharyngioma [38]. In contrast, a hypocaloric diet in a child with ROHHAD-NET syndrome did not result in weight loss [27]. These findings indicate that a hypocaloric diet, and a diet incorporating a restriction in macronutrients such as low carbohydrates, may be effective in children with PWS and craniopharyngioma. Given the features of HO, like hyperinsulinemia and lower energy expenditure, a diet targeting both (hypocaloric diet also including restriction in carbohydrates), is considered a plausible effective intervention.

Out of the four studies on lifestyle interventions, all showed stabilization or decrease of BMI on short-term [39–41,44]. A combined lifestyle program including a nutritional course, resulted initially in weight loss in children with MC4R mutation, however, their BMI SDS returned to baseline values two years after the intervention. This finding illustrates that lifestyle programs may be effective on short-term but it is difficult for children to comply to this lifestyle on long-term [39]. A combined intensive 1-year

Table 4
Summary of results on feasibility and safety.

Reference	Subjects and diagnosis (n)	Age (y)	Study design	Dietary/lifestyle intervention	Outcome on feasibility	Outcome on safety
[34] Miller et al., 2013	Prader–Willi syndrome (n = 63), n = 33 in the intervention group	2–10	Intervention, as part of prospective longitudinal cohort study	Energy restricted diet with well-balanced macronutrient composition (30% fat, 45% carbohydrates, 25% protein, >20 g fiber); feedback of dietitian after receiving dietary records	33 children complied to the energy restricted and well-balanced diet (intake: 25–30% fat, 40–50% carbohydrates, 20–30% protein, 14–26 g fiber), while 30 children did restrict energy intake to REE but did not alter dietary composition (intake:10–23% fat, 50–70% carbohydrates, 15–20% protein, <12 g fiber) Non-compliance related to difficulties with lowering the carbohydrate intake. Decreasing fat intake was easier than decreasing carbohydrates in diet	NA
[35] Felix et al., 2020	Prader–Willi syndrome (n = 7)	6–12	Clinical feasibility study	Modified Atkins diet (10–15 g net carbohydrate limit, pediatric multivitamin, vitamin D and calcium supplement, protein/fat on individual basis)	4 children completed the full 4-month diet intervention (2 children were unable to comply, 1 child was excluded because of an elevated urine calcium/creatinine ratio).Children who completed reported that it was tolerable and parents saw drastic changes in their child's attitude toward food	The diet did not affect linear growth
[42] Bonfig et, 2009	Prader–Willi syndrome (n = 5)	14–19	Intervention without control group	Strict fat-reduced, and carbohydrate-modified diet (10 kcal/cm/day; 25% protein, 20% fat, 55% modified carbohydrates)	NA	Hematologic and chemistry data remained normal. No psychological symptoms or mood changes occurred.
[36] Lima et al., 2016	Prader–Willi syndrome (n = 5)	6–16	Intervention without control group	Hypocaloric diet (10 kcal/cm/day, starting with 14 kcal/cm/day for maintenance and 7 kcal/cm/day for weight loss; grains 150 kcal; vegetables 15 kcal; fruits 35 kcal; legumes 55 kcal; meat/eggs190 kcal; dairy 120 kcal)	It was difficult to comply to the diet because of hyperphagic behavior, but all succeeded	The diet did not affect linear growth
[37] Irizarry et al., 2019	Prader–Willi syndrome (n = 8), but only n = 2 patients had a BMI SDS >2.0, the other children were normal weight	9–18	Intervention with cross-over design	Two diets: carbohydrate restriction and fat restriction during a 72h hospital admission (low carb: 15% carb, 65% fat, 20% protein vs low fat: 65% carb, 15% fat, 20% protein; 80% of EER according to age/gender; daily multivitamin)	NA	Higher inflammatory markers and elevated AST and ALT after carbohydrate-restriction
[43] Holm et al., 1976	Prader–Willi syndrome (n = 14)	1–18	Intervention without control group	Weight control program (8–9 kcal/cm/day; 15–20% protein, remaining fat and carbohydrates)	3 children did not sneak food, the others all did (most common serious problem). Other problems listed were: gorging foods, consumption of unappealing products, obsession with refrigerators, worrying about food, and preoccupation with food and eating.	The diet did not affect linear growth
[38] Lee et al., 1992	Craniopharyngioma (n = 1)	14	Case report	Protein-sparing modified fast (567 kcal/day, 71g protein, 27g fat, 10g carbohydrates; daily supplementation vitamins and minerals)	NA	The diet did not affect linear growth
[27] Marpuri et al., 2022	ROHHAD-NET syndrome (n = 1)	6	Case report	Caloric restriction (≤1000 calories/day) and macronutrient plan of ≤100 g carbohydrates daily	NA	NA

[39] Reinehr et al., 2009	MC4 receptor mutation (n = 16)	5–16	Intervention trial in 2 groups with obesity: with mutation and without mutation (control group)	1-year lifestyle intervention including parents course, behavior therapy, talk rounds, nutritional course, individual psychological therapy, exercise therapy. Nutritional course on 'optimized mixed diet' (30% fat, 15% proteins, 55% carbohydrates) + 'traffic-light system'	Of the 16 overweight children, 9 (56%) did not complete the motivation phase before the intervention. One child dropped out during the intervention period.	NA
[40] Hainerová et al., 2007	MC4 receptor mutation (n = 4)	13–17	Intervention trial in 2 groups with obesity: with mutation and without mutation (control group	6-week lifestyle program including: physical exercise of 4 h/day, energy-restricted diet (fat ≤30%, carbohydrates 50–55%, total energy 5–7 MJ/day) + education and psychologic support	NA	NA
[41] Trier et al., 2021	MC4 receptor mutation (n = 24)	2–19	Intervention trial in 2 groups with obesity: with mutation and without mutation (control group)	Low intensity individual lifestyle program including eating behavior, physical activity, sources and amount of nutrition, psychosocial functioning, sleep pattern	NA	NA
[44] Morell-Azanza et al., 2019	MC4 receptor mutation (n = 7)	8–14	Randomized controlled trial	1-year lifestyle intervention including a hypocaloric Mediterranean diet + exercise of 200 min/week	NA	NA

lifestyle intervention of 200 min exercise per week with hypocaloric diet showed reduction of BMI SDS compared to baseline after eight weeks, but again this was not sustained after 1 year [44]. This indicates that children with HO need intensive continuous support with lifestyle interventions. Lifestyle support in children with HO is needed to improve their cardiorespiratory endurance [6].

In addition to the studies retrieved by our search and snowballing, one additional study was identified online (Thesis chapter) but was not published in the databases assessed in this review. This study reported on an individualized dietary intervention for children with suprasellar brain tumors and HO. A dietary plan (called 'dot-plan') was assessed using 7–8 kcal/cm/day. This intervention was considered feasible and resulted in BMI decrease in five out of six children at 9 months after start of intervention. However, after 12 months, BMI returned to baseline in most patients, and only two patients showed reduction of BMI (−0.19, −0.14, respectively) [50].

In addition, although this was not the scope of our review, next to treatment of hypothalamic overweight or obesity, it is of course even more effective to try to prevent weight gain in children at risk for (hypothalamic) obesity. As discussed in the introduction, children with PWS and low-grade glioma may change from having underweight to overweight at two and four years of age, respectively [13,14]. Indeed, a previous study with a strict fat reduced and modified carbohydrate intake (10 kcal/cm/day) in nine children with PWS, starting at the age of 1–2 years while the children still had a normal weight, could prevent weight gain in the treatment group compared to the control group, with the control group developing a BMI SDS of +1.8 SDS at the age of two years, while the intervention group could remain a BMI of −0.1 SDS. After 10 year follow-up the treatment group had a mean BMI SDS of +1.2 SDS compared to +2.4 SDS in the control group [51]. In addition to diet, introduction of growth hormone therapy for PWS has greatly diminished the prevalence of obesity in this group [52]. In children with craniopharyngioma a, treatment with GH may improve longitudinal growth but its effect on obesity development is disappointing [53]. Our systematic review specifically focused on the effect of dietary or lifestyle interventions on weight or BMI in children with HO. Some previous (case)studies evaluated the effect of other interventions such as evaluation of incorporating a multidisciplinary approach in care for children with suprasellar brain tumors at risk for hypothalamic obesity. Weight gain in terms of BMI SDS increase and kg/month were significantly lower in the group treated in a multidisciplinary team compared to standard care [54,55]. In addition, a case study highlighted the importance of a strong home-environment to help fighting weight gain [56].

Next to its effect on BMI, the studies identified in this review also reported on other outcomes such as body composition. The only study reporting on the effect on body composition (restricted well-balanced diet, 30% fat, 45% carbohydrates, 25% protein, 20g fiber per day) reported an improvement in body composition, with lower percentage of fat in children adhering to the diet, however this finding was not significant when corrected for carnitine and co-enzyme Q10 supplements, nor did the authors correct for physical activity [34]. Higher fat-free mass (and thus higher muscle mass) can positively contribute to resting-energy expenditure and therefore promote further weight loss [57].

Another interesting outcome for future studies could be the gut microbiome, which may have an interesting relationship with weight gain. Previous studies on dietary modulation (rich in non-digestible carbohydrates) of the microbiome resulted not only in weight loss but shifted the dysbiotic gut microbiota to a healthier structure in patients with obesity and PWS [58]. Low-carbohydrate diets have shown conflicting effects on the gut microbiome, both positive and negative [33]. Further research on this topic is needed.

Considering the fact that hyperinsulinemia may play a role in the pathophysiology of hypothalamic overweight or obesity, diets low in carbohydrates may be successful for lowering body weight in these patients. One of the most extensive carbohydrate restrictions is a ketogenic diet [59]. Currently, ketogenic diets are increasingly being used for children and are successfully applied for example in children with refractory epilepsy [60]. The effect of ketogenic on linear growth in children remains a matter of debate [61]. Three studies included in our systematic review may be classified as having studied a ketogenic diet [35,37,38] and two of them showed a positive effect on weight. In these three studies, no effects on growth were reported. A study on a carbohydrate restricted diet (ketogenic) showed elevated liver enzyme values, however the clinical implications of these findings were not evaluated in this study [37].

Despite our efforts to formulate a sensitive search, the majority of the articles identified in this systematic review were identified via snowballing. This may be caused by the absence of the keyword 'hypothalamic' in title or abstract, for example if only PWS or a specific mutation was mentioned. Extensive snowballing was performed and the search was repeated in adults to confidently capture all relevant articles. Importantly, most of the studies we identified were performed in children with PWS or monogenic obesity. Although there are similarities with children experiencing HD after treatment for a brain tumor, it does affect the generalizability of this review to children with acquired hypothalamic dysfunction. One of the main differences is that children with PWS often do not experience hyperinsulinemia but rather hypoinsulinemia followed by hyperghrelinemia [62].

Moreover, due to heterogeneity between study groups, it was not possible to perform a pooled analysis. Conclusions must be drawn with caution due to high risk of bias in all but one of the studies. Only one study was a randomized controlled trial. Despite these limitations, this is the first systematic review on dietary interventions for children with hypothalamic overweight or obesity, summarizing all relevant information on dietary and lifestyle interventions for this patient group. Knowledge on which diet and lifestyle to advice to children and adults with hypothalamic overweight is essential aiming to prevent worsening of BMI at an early stage, and subsequent cardiovascular and metabolic consequences. Lifestyle and diet remain the cornerstone of treatment in addition to potential new pharmacotherapeutic approaches.

5. Conclusion

There is a paucity of evidence on the most optimal diet and lifestyle for children with hypothalamic overweight or obesity. With a very low to low quality of evidence, it may be concluded that a hypocaloric diet or a well-balanced restrictive macronutrient diet is feasible, has no safety concerns regarding longitudinal growth, and may help to lose weight. Next to this, also lifestyle programs have shown promising effects in BMI reduction on short-term for hypothalamic obesity, however intensive support is needed to maintain the succeeded weight loss on long-term to make it feasible. Since the lack of quality and quantity of studies, larger prospective studies comparing a dietary/lifestyle intervention with standard of care, including an appropriate control-group, are warranted. Given the complex facets of HD, implications on the psychological sphere and general nutritional status of children should also be included into future studies.

Registration and protocol

The review was not registered and a protocol was not prepared.

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Availability of data

All data extracted from the included articles is publicly available.

Author contributions

IMAA van Roessel: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing original draft.

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WJE Tissing: conceptualization, investigation, methodology, visualization, writing review & editing.

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Conflict of interest

None of the authors report a conflict of interest.

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Appendix A. Supplementary data

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