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Abstract

Aims: Children with obesity are treated by a lifestyle intervention to obtain weight loss. Nevertheless, weight regain often occurs. This systematic review examines the effect of weight regain on cardiometabolic health and summarizes these results in the metabolic syndrome prevalence as integrated endpoint.

Data synthesis: A literature search was performed in PubMed and Web of Science. Studies were selected if they included participants aged <18 years with obesity and presented data before and after weight loss and after weight regain hereby reporting minimally 1 cardiovascular risk factor at every assessment. After screening, nine articles remained.

Generally, the diastolic BP re-increased after weight regain, whereas for systolic BP a sustained result for 6 months was reported with an increase during longer follow-up. No significant changes in fasting glucose were reported after weight regain compared to baseline. Regarding triglycerides, a complete weight regain re-increased the lowered values to baseline, whereas a partial regain resulted in a sustained decrease in triglycerides in 2 studies and an increase to intermediate levels in 1 paper. HDL-cholesterol only rose several months after initiating treatment. Hs-CRP remained lowered for a longer period than the moment where the weight loss nadir was achieved.

Conclusion: Research on weight regain and cardiometabolic health in children with obesity is scarce. No convincing evidence was found for a worsening of the cardiometabolic profile after weight regain. Some benefits even persisted despite weight recovery. Subsequently, the metabolic syndrome prevalence seems temporarily lowered after weight loss, despite weight regain.

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Keywords: pediatric obesity; cardiometabolic health; cardiovascular risk factors; metabolic syndrome; weight regain.

Introduction

Anno 2016, worldwide 124 million children aged 5 to 19 years old were classified as obese.[1] Obesity even in childhood is associated with multiple co-morbidities, including sleep apnea, liver steatosis, polycystic ovarian syndrome, endothelial dysfunction...[2–4] Furthermore, up to 70% of the children with obesity have at least one cardiovascular risk factor, including an elevated triglyceride level, LDL-cholesterol, fasting insulin or blood pressure and a lowered HDL-cholesterol.[5] A clustering of multiple risk factors is referred to as 'the metabolic syndrome'. The last decades multiple attempts to define the metabolic syndrome in pediatrics have been made.[6–8] Interestingly, these definitions all rely on the same key features, e.g. central obesity (mostly defined by the waist circumference),

triglyceride elevations, a lowered HDL-cholesterol, arterial hypertension and a disturbed glucose tolerance, however the cut-offs of normality might vary strongly depending on the definition used. Additionally, the complexity even further increases as the role of ethnicity comes in. Ethnic differences in a persons' vulnerability to develop certain cardiometabolic problems exist.[9] As a consequence, the developed definitions are population-specific and different threshold values must be used for different ethnic groups, e.g. the IDF definition is applicable to a European population specifically.[6]

The past few years, the diagnostic value of the metabolic syndrome in pediatrics has been questioned. The reasons for this debate are: the missing of one universally accepted definition, the criteria relying on a categorical (yes/no) fulfillment whereas the clinical risk factors are continuous variables, the instability of the diagnosis throughout the development to adulthood despite the consistent clustering of risk factors and the conflicting results regarding the predictive potential towards adulthood metabolic syndrome and adverse health consequences.[10–15] Therefore, the American Academy of Pediatrics recommends to 'shift the focus to cardiometabolic risk factor clustering'. Hereby, they advise to focus more on screening of the individual risk factors and to be aware that the presence of one cardiometabolic risk factor is often accompanied by other risk factors.[16]

Besides the classic risk factors linked to cardiovascular disease, lately attention is drawn to non-classic risk factors, including low-grade inflammation.[17] Hs-CRP has previously been found to provide prognostic information on the occurrence of cardiovascular disease and mortality, even after controlling for multiple variables.[18] As children with obesity are at increased risk to become adults with obesity[19,20], subsequently the clustering of cardiometabolic risk factors, in the past referred to as the metabolic syndrome, often tracks

from childhood into adulthood[21] and is associated with a (two-fold) increased risk on developing cardiovascular disease or a five-fold increased risk to develop type 2 diabetes.[22–24]

The cornerstone of treating obesity in pediatric populations remains a lifestyle intervention aimed at losing weight by reducing caloric intake and increasing physical activity.[25] Outpatient behavioral interventions can give a small but significant reduction in BMI of 1-3 kg/m^2, although drop-out rates are high.[4] Inpatient programs result in an average weight reduction of 15 kg or 4.5 kg/m^2 in BMI.[26] However, in the long-term, weight regain is often the reality[27–31], especially in those with severe obesity.[32]

In literature, weight loss followed by weight regain is often named as weight cycling or yoyo-dieting[33] and has been associated with increased cardiovascular morbidity and mortality. In the Framingham population, an association was found between the coefficient of variation (CV) of body weight and cardiovascular morbidity and mortality[34] and another study in middle-aged men reported that the group reporting large weight gains and large weight losses had a doubled relative risk of coronary heart disease related death when compared with the weight stable group.[35] Rzehak *et al.* reported an association between all-cause mortality and weight fluctuations in 55-74 year old men, which was not present for stable-obese or stable non-obese participants.[36]

To explain these increases in cardiovascular risk, the repeated overshoot theory was developed, stating that on the moment of weight regain multiple cardiovascular risk factors transcend their baseline values and hereby negatively influence cardiovascular health.[37]

Recent publications show that yoyo-dieting increasingly occurs in children and adolescents.[38]

Most studies in children with obesity report the effect of a weight-loss intervention at the end of treatment. Although these results are interesting, we need to face the reality of quick weight regain. Therefore, we have reviewed the existing literature on the influence of weight loss and weight regain on the different cardiovascular risk factors separately. Secondly, we have provided a general synthesis by discussing the influence of these weight changes on the metabolic syndrome, as a surrogate endpoint for the combined cardiometabolic risk profile.

Methodology

We performed a systematic review according to the recommendations of the PRISMA guidelines.[39]

Eligibility criteria

Studies were included if the following criteria were met:

- mean age < 18 years old
- mean BMI defined as obese by recognized international criteria
- research reporting data before and after weight loss, followed by a period of longitudinal follow-up in which any form of BMI regain occurred
- information on at least 1 cardiometabolic risk factor at every time point
- written in English, French, Dutch or German

Only original clinical studies were included. Publications were excluded if they consisted of literature reviews, if only adults or animal models were included, and/or if an endogenous cause for obesity was studied.

Search strategy

A literature research was performed in Pubmed and Web of Science using the following search strategy: ((("obese children" or "obese adolescents" or "pediatric obesity" or "obese teenagers")) AND (“body weight trajectory” or “body mass index trajectory” or “body mass index change” or “body weight change” or “weight cycling” or “weight regain” or “body mass index regain” or “body mass index cycling” or “yoyo-dieting” or “post-dieting weight regain” or “body mass index variability” or “weight variability” or “weight maintenance”)) AND ("cardiovascular diseases" or “cardiovascular risk” or "hypertension" or “blood pressure” or "vascular function" or "endothelial dysfunction" or "vessel disease" or "cardiovascular risk" or "cardiovascular health" or "inflammation" or “hs-CRP” or "cholesterol" or “triglycerides” or “HOMA-IR” or “endothelial function” or “endoPAT” or “reactive hyperemia index” or “cardiac” or “insulin resistance” or “impaired glucose tolerance” or "fasting glucose" or "fasting insulin" or "HDL-cholesterol" or "LDL-cholesterol" or "total cholesterol" or “diabetes type 2” or “IL-6” or “IL-10” or “inflammatory cytokines”). This search was last repeated on March-9-2020. When a reference in a selected paper pointed to another relevant study, these references were searched manually (snowball effect).

Study selection

The 'template for study selection' created by the 'KCE - Belgian Health Care Knowledge Centre' was used for synthesizing the result of the selection process. Relevant studies were selected in 3 stages. First, duplicates were removed. Second, publications were screened on title and abstract. Then, when the paper was found relevant and met the eligibility criteria, the full text version was screened and, if it fulfilled the criteria, included in the systematic review. If there was doubt over the eligibility of a publication, a second reviewer was consulted.

Data extraction

The following information was extracted from each paper: patient characteristics (e.g. number of patients, patient eligibility criteria), study design, the amount of weight lost and regained and the cardiometabolic risk factors studied.

Risk of bias

The risk of bias in each individual study was assessed by the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Institutes of Health (NIH).[40] Based on a list of 14 items, this tool evaluates the following parameters: the study objective and population, the study design, the statistical analysis and power of the study and the risk of bias. At the end of the checklist, the overall quality of the study was rated as good, fair or poor based on the 14 items by the rater.

Results

Literature search

A systematic search in Pubmed and Web of Science resulted in 93 articles. Eleven studies were found eligible and another 3 studies were added by hand searching the reference lists of the selected papers. Eighty-two articles were excluded based on title and abstract. Thirty-nine papers were excluded because of their design, as they were reviews or based on cross-sectional research. The interventional papers excluded showed a longitudinal follow-up, but did not report weight regain data. Finally, 15 articles were evaluated in full text. Additionally, 5 studies were excluded after full reading for the following reasons: two studies did not report a cardiovascular risk factor at follow-up and three studies only reported weight loss, but no weight regain. At the end of the selection process, 9 articles met the eligibility criteria. (Figure 1)

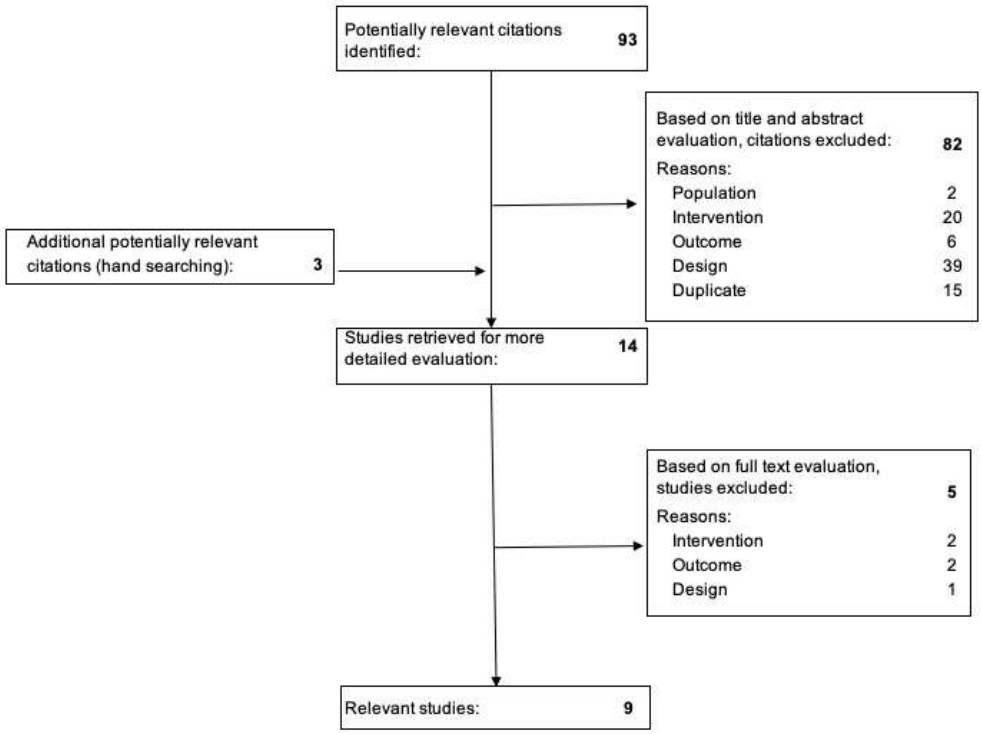

Figure 1: Flowchart of the study selection for inclusion in the review

Study characteristics

Of the 9 selected studies, 4 were randomized controlled trials (RCT) comparing two treatments[41–43] or a treatment with a control group[44]. Four studies were prospective observational studies [29,45–47]and one was a retrospective descriptive case series.[48] An overview of the extracted information can be found in Table 1.

A total of 651 children and adolescents with obesity were included in this review. The mean age was 9.8 years. Two papers comprised the same patient cohort, so these patients were only counted once.[45,46] Kelishadi *et al.* did not report the male-to-female ratio.[41] Of the remaining 551 participants, 264 were female (48%). The study of Holm *et al.* comprising 115 patients only reported BMI SDS, which was 3.0 SDS.[45] The average BMI of the other 536 patients was 26.5 kg/m^2. Three studies were performed in pre-pubertal children with obesity, with one including also children with overweight. Two studies included both children and adolescents aged 8 – 15 years old. Four studies were conducted in adolescents, age ranging from 12 to 19 years, with two studies reporting only on adolescents with severe obesity.

Only 3 papers focused specifically on the influence of weight regain after weight loss[29,45,46], whereas the remaining 6 papers presented these data, without weight regain being one of the primary or secondary outcomes of that particular study. Most studies focused on lifestyle interventions for obtaining weight loss. The lifestyle intervention studies consisted of an outpatient setting in 4 studies[41–44] and an inpatient setting in 3 studies[29,45,46]. Just two studies discussed the influence of a surgical weight loss intervention.[47,48] Six papers reported information on blood pressure[41–43,45,47,48], 7

on the metabolic profile (cholesterol, lipids, glucose, insulin) [29,41–44,47,48] and 3 on the inflammatory profile.[42,43,46]

Quality of the evidence

An overview of the quality assessments of the studies can be found in the supplementary material (see Table S1). Most studies included had a suboptimal quality. The most common limitations were small sample sizes and high or unreported drop-out rates. Additionally, some studies made no statistical comparison between the baseline and follow-up data. A control group with maintained weight loss was only present in 1 study.[29]

Summary of the results

Due to the heterogeneity of the included studies, a meta-analysis could not be performed. Therefore, a qualitative synthesis of the main results is given structured by the cardiometabolic outcome parameters as summarized in Table 2.

Body composition

Three studies reported information on body composition[29,42,47]. Two studies reported on fat% as a parameter for body composition[42,47], whereas Lazzer and colleagues reported the fat and fat-free mass, but this allows to calculate fat% indirectly. [29]

The fat% decreased significantly by all three interventions and increased thereafter. In two out of three studies - where patients partially and completely recovered their lost weight - the fat% remained significantly under baseline levels [29,42]. In the study of Sachdev *et al.*

the fat% recovered to a non-significant difference with baseline levels (p=0.5), however here patients regained more than double of their initially lost BMI points.[47]

Waist circumference

Five studies reported on waist circumference. [41–43,47,48] and all reported a significant decrease in waist circumference after treatment. [41–43,47,48]

A near complete weight regain and more than complete weight regain was observed in the studies Okely *et al.* and Shalitin *et al.*, with a difference from baseline of 0.1 kg/m^2 decrease and +0.3 kg/m^2 increase in BMI, respectively. [42,43] The waist circumference equaled pretreatment circumference in the first study, whereas it exceeded the initial measurement in the second study. The sample size of 10 participants (that regained double of their lost BMI) in the study of Sachdev and colleagues might have been too low to detect a statistical significant increase in the waist circumference, however a clear trend is found with an average increase in waist circumference of 10.4 cm from baseline (p=0.3).

A partial weight regain, observed by Kelishadi *et al.* did not significantly increase waist circumference compared with the waist circumference measured right after treatment.[41] In the study of Franco *et al.*, patients with a sleeve gastrectomy lost 60% of their excess weight but regained 15% after 24 months. The waist circumference remained lower than baseline, but was significantly higher than the point with a 60% excess weight loss.[48] The average post-treatment BMI increase was more pronounced in the group of patients that underwent a sleeve gastrectomy than in the prepubescent children treated by a lifestyle intervention as described by Kelishadi *et al.* This difference in BMI increase after treatment

294 provides an explanation for the difference in results regarding the effect of partial weight
295 regain.
296
297 Waist circumference generally seems to parallel the amount of regain.
298
299 *Blood pressure*
300 Six studies investigated the effect of weight changes on blood pressure[41–43,45,47,48],
301 whereas two studies did not report a change in blood pressure.[43,47]
302
303 Kelishadi *et al.* reported a significant decrease in SBP by -1.7 $\pm$ 0.5 mm Hg in prepubertal
304 children after a 6-month weight loss program in both a diet and an exercise group with a
305 weight loss of 1.1 and 1.04 kg/m^2. This benefit was sustained 6-months after the
306 intervention, despite that half of the lost weight was regained. The DBP did not change
307 significantly throughout this study. [41]
308
309 The study of Holm *et al*. was designed specifically to assess the effect of weight loss followed
310 by weight regain on blood pressure. They described a divergent response for DBP and SBP
311 SDS after weight regain studied in children with obesity aged 8 – 15 years old after a 3-
312 month inpatient weight loss program.[45] The lowest DBP was measured at the end of the
313 treatment program and DBP started to increase immediately and proportional to the
314 increasing BMI. Contrarily, the lowest SBP was found 13 months after ending the program,
315 despite a weight regain of 0.5 BMI SDS at that time. SBP increased between 13 months and 2
316 years after ending the weight reduction program, but 2 years after treatment, both DBP and

SBP did not reach the hypertensive values as seen at baseline, although the participants' weight was exceeding baseline weight.[45]

In a sleeve-gastrectomy study performed in adolescents with severe obesity, the number of patients with arterial hypertension decreased from 59.1% (13/22) to 17.6% (3/17) 1 year after surgical intervention. Two years after gastric sleeve 21.4% of the patients, corresponding to 3 out of 14, were diagnosed as hypertensive, however it was not stated whether these 3 patients were the same as the 3 hypertensive patients reported 1 year post-gastrectomy.[48]

In the study of Shalitin *et al.* the DBP evolution followed the BMI evolution, with a significant decrease during treatment and a reincrease to baseline thereafter. In this study conducted in prepubertal children, the SBP was not initially lowered by the 3-month intervention. Remarkably, in the exercise-only group was reported to have a significant increase between the SBP values 9 months post-intervention compared with those at baseline ($p<0.05$), with an SBP of 114 ± 2.7 mm Hg at follow-up compared to 110 ± 2.2 mm Hg at baseline. The DBP did not change significantly throughout the study.[42] It has to be noted that both age and height increased as well by the last study visit, which are known confounders of blood pressure.[49] Secondly, diet can also influence blood pressure, for example by salt or protein intake or energy drinks[50] and since the exercise group was not provided with any dietary advice, this might contribute to the increased blood pressure registered at follow-up.

In summary, the three studies reporting a decrease in SBP after weight loss, all found a sustained benefit 6 months after the intervention[41,45,48]. Although, two studies reported a re-increase during a longer follow-up of 12 and 25 months compared to the blood pressure at the weight loss nadir.[45,48] Regarding DBP, two studies reported a weight loss induced lowering, that increased with weight regain compared to the weight loss nadir. Shalitin *et al.* reported that the DBP returned to baseline levels after complete weight regain, whereas Holm *et al.* reported that the percentage of subjects with a SBP or DBP SDS above the 90th centile was still lower than measured initially despite full weight recovery.[42,45] Neither systolic nor diastolic blood pressure were found to overshoot baseline values, even when weight was fully regained. Furthermore, evidence even seems to indicate a potential prolonged benefit on the systolic blood pressure.

Inflammatory profile

Only 3 studies reported on the inflammatory profile, with all including data on hs-CRP.[42,43,46] Two studies reported no significant changes in hs-CRP by weight loss or regain.[42,43]

Lausten-Thomson *et al.* focused specifically on the influence of weight loss and weight regain on hs-CRP. They found that hs-CRP tended to decrease during a 3-month inpatient weight loss program and increased again after weight regain. However, the concentrations of hs-CRP measured roughly 6 and 12 months after inpatient treatment were comparable to those measured at the end of the weight loss program, despite that the patients' BMI had already increased by that time. The authors hypothesized that the body might require some

time after weight regain before the baseline inflammatory state is restored. Nevertheless, the concentration of hs-CRP was associated with BMI SDS during the period of weight regain, with an increase of 1 BMI SDS being associated with an increase of 60% in hs-CRP in boys and 88% in girls.[46]

Insulin and glucose metabolism

Four studies found a beneficial effect of weight reduction on fasting insulin, fasting glucose and/or insulin (resistance indices)[29,43,44,48], while two did not.[41,47] One study reported a beneficial effect only on fasting blood glucose, but not on fasting insulin or HOMA-IR.[42]

In the studies of Chang *et al.* and Shalitin *et al.*, all the lost weight was completely regained.[42,44] Chang *et al.* studied 49 children with a mean BMI reduction of 0.6 kg/m^2 after a 9-month supervised exercise intervention. BMI increased significantly over baseline values 3 months after the intervention with the fasting insulin, fasting glucose and the HOMA-IR returning to baseline levels.[44] The RCT of Shalitin *et al.* found a significant decrease of blood glucose levels after the weight loss intervention, that returned to baseline values at follow-up, but with no significant difference between the different RCT-groups, e.g. diet, exercise or the combination of both. The fasting insulin levels and HOMA-IR did not improve during weight loss intervention, but after weight regain, a significant increase above baseline values was reported.[42] However, this latter study was conducted in preadolescent children, and at follow-up 26 of the children had entered puberty. Since in

puberty, all children develop some insulin resistance[51], this might have contributed to the increased fasting insulin and HOMA-IR measured at follow-up.

In two studies, patients partially regained their lost weight after a lifestyle intervention. The RCT of Okely *et al.* consisted of a parent-centered dietary program, a child-centered physical activity program or both offered face-to-face for 10 weeks extended with a relapse prevention program for 3 months provided telephonically. The first follow-up visit was planned immediately after the relapse prevention program (so 6 months from baseline) and the second visit 6 months after ending the telephonic follow-up (so 12 months from baseline). Patients lost on average 0.6 kg/m^2 at 6 months and regained 0.5 kg/m^2 by 12 months, which caused no significant changes in fasting glucose, but resulted in an improved fasting insulin 6 months from baseline, which was sustained until 12 months from treatment start, despite weight regain.[43] A 9-month inpatient weight reduction program, as described by Lazzer *et al.,* that resulted in an average weight loss of 6.3 kg/m^2, significantly improved the patients' fasting glucose and insulin levels.[29] However, in both groups, e.g. patients that maintained the weight loss and in those that regained weight, an increase in fasting glucose to baseline levels and insulin to intermediate levels was registered after 4 months follow-up.

The highest weight loss was obtained by a sleeve gastrectomy. On average, patients lost 34.5 kg or 12.3 kg/m^2. Despite a partial weight regain of 39%, the improved metabolic profile was maintained at least up to 2 years after surgery. One patient with type 2 diabetes reached remission and 2/3 of the insulin resistant patients (defined as HOMA-IR>2.5) normalized their insulin values.[48]

Altogether, none of the studies reported a significant difference in fasting glucose after weight regain compared with baseline. Regarding fasting insulin, one study where weight was completely restored, reported no difference with baseline after weight regain.[45] Two out of three studies with a partial weight regain reported a sustained ameliorated insulin sensitivity[43,48] and one mentioned an increase to intermediate levels.[29]

Lipid and cholesterol disturbances

Regarding triglycerides, 2 studies found no changes after weight loss or weight regain[43,47], however 5 other studies reported a significant decrease of triglyceride levels after weight loss.[29,41,42,44,48] This improved lipid profile was maintained despite a partial weight regain in the studies of Kelishadi *et al.* and Franco *et al.,* measured 6 months after a lifestyle intervention and 24 months after sleeve gastrectomy compared to the moment with the lowest BMI, e.g. at the end of the lifestyle intervention and 6 months after surgery.[29,41] In contrast, Lazzer *et al.* reported that the triglycerides significantly increased to intermediate levels in 10 patients who partially regained weight after an inpatient weight loss program.[29] A complete weight regain measured 3 and 9 months post-intervention, returned the triglycerides to baseline levels in the RCT's of Chang *et al.* and Shalitin *et al*. [42,44] Therefore, the BMI difference from baseline seems an important determinant of (longer term) triglyceride profile.

Two studies found no effect on LDL-cholesterol in response to weight loss or weight regain. [41,44] In contrast, an inpatient intervention did lower the LDL concentrations significantly,

but this reduction was not maintained after partial weight regain and returned to initial values. Furthermore, the changes in LDL-cholesterol were related with the changes in BMI and fat mass during the period that the weight was regained ($r=0.6$ and $r=0.57$, $p<0.05$).[29] Okely *et al.* reported a significant increase in LDL-cholesterol 6 months after their weight loss intervention, targeted at diet, exercise or both, compared to baseline ($p=0.02$), although the change was small, e.g. 0.17 mmol/l (0.02-0.31). At this moment, patients had almost completely recovered their lost weight.[43] A 12-week intervention consisting of exercise, diet or the combination, did not lower significantly the LDL-cholesterol, although a non-significant diminishment in the cholesterol values was yet observed. At 9 months follow-up, a further decrease in LDL-levels was observed resulting in a significant difference from baseline ($p<0.01$). The decrease in BMI SDS during the entire study related significantly to the change in LDL-cholesterol ($r=0.281$, $p=0.037$).[42] In summary, a highly heterogenic response of LDL-cholesterol in reaction to weight changes is seen across the cited studies. Although the correlations found by Lazzer and Shalitin between BMI and LDL-cholesterol suggest a role for overall weight reduction of regained body weight from the weight loss nadir.

HDL was not increased by any of the lifestyle interventions immediately after ending treatment. Surprisingly, three studies found an increase in HDL levels 12 months after starting the weight loss intervention compared to the end-intervention levels despite a partial or complete weight regain.[29,42,44] Franco *et al.* described the effect of a sleeve gastrectomy and found an increase in HDL, already starting 6 months after surgery. This significant improvement in HDL was sustained for at least 24 months.[48] As HDL cholesterol

458 is said to ‘typical respond slowly to body weight changes’[44], these results confirm this
459 hypothesis, despite the occurrence of weight regain.
460
461 **Discussion**
462 This systematic review summarizes the current literature on the effects of weight regain
463 after weight loss on different the components of the metabolic and cardiovascular risk
464 profile in obese children. There is no clear evidence pointing towards a harmful effect of
465 weight regain after weight loss. Whereas certain risk factors increase in line with the weight
466 recovered, others seem to experience a prolonged benefit of the preceding weight loss.
467 Although based on the current evidence, we cannot determine how long this benefit persists
468 and what happens on the long term by weight regain.
469
470 Since the metabolic syndrome represents a common clustering of all these separate risk
471 factors, except for the pro-inflammatory status, this is an interesting surrogate endpoint to
472 estimate the influence on the combined cardiometabolic risk profile. A recent review
473 reported a metabolic syndrome prevalence in children and adolescents ranging from 0.3 –
474 26.4% depending on the definition used and the population studied.[52] Miller et al.
475 reported that 73.2% of the US adolescents has at least one cardiometabolic risk factor[53],
476 with central obesity and dyslipidemia (low HDL or high triglycerides) being the most
477 prevalent features.[52,54] As the increase in HDL seems to be sustained for a longer period
478 after weight regain, this sustained benefit could result in a decreased prevalence of the
479 metabolic syndrome despite weight regain – independent of the definition used. This
480 delayed response to weight regain was also observed for hs-CRP in both a pediatric and an
481 adult study.[46,55] Both, HDL and hs-CRP are secreted by the liver and response to changes

in the adipose tissue, although indirectly.[56,57] Therefore, when weight regain leads to a complete restoration of the lost visceral adipose tissue, a period of time exists between the weight recovery and the changes in hs-CRP and HDL. An additional explanation for the late response of HDL to weight changes can be found in the hypothesis that weight loss and weight regain favor the visceral adipose tissue depot[58], whereas subcutaneous tissue is likely the most important contributor to the circulating HDL-cholesterol concentrations.[57] This might explain the different reaction to weight changes compared to the other risk factors that are more directly influenced by the visceral adipose tissue, for example blood pressure by the adipocytes producing leptin and angiotensinogen[59].

Our results are consistent with findings in obese adults. Li *et al.* reported that patients that restarted a weight loss program had a lower blood pressure and lower triglycerides than the first time they participated, despite they had regained 73% of their lost BMI at that time.[60] Graci *et al.*, studying weight cycling in adults with obesity, stated that it is more the accumulation of body fat over several years rather than the weight cycling or weight regain that negatively affects cardiovascular health and body composition[61]. This is in line with the findings of Wing *et al.* that it is rather the netto weight loss or weight gain than the trajectory taken that determines the cardiovascular profile.[62] It should be noted that children with obesity often already have one or more cardiovascular risk factors. Therefore, weight reduction might temporarily improve their health status, independent of the weight regained. This is an important difference with their normal-weight counterparts that are in good cardiovascular health and subsequently an important difference with the population included in the large cohort studies describing an adverse effect of weight regain on cardiovascular health.

Although, our results are consistent with those reported in adults, the results should be viewed with the following limitations. First, all included studies had a rather low sample size ranging from 12 to 162 subjects. Additionally, high drop-out rates were often present without a clear description of the population that dropped-out. Secondly, a high heterogeneity was found between studies for the type of intervention, the duration of the intervention and subsequent follow-up, the amount of weight loss and weight regain, and the evaluated outcome measures. Additionally, there is no straightforward definition of weight cycling available in children, as multiple authors use different definitions.[33,63] In this review, we have used absolute BMI change as a reference, since BMI Z-score might not reliably report the influence on the true BMI trajectory and has limitations in children with severe obesity as pointed out previously.[64,65] A good example hereof is the study by Okely *et al.*, where both BMI and BMI Z-scores are reported. When studying the results as BMI data, a weight regain is seen between 6 and 12 months. However, studying the same data as BMI Z-score shows a stable or even a decrease in weight trajectory.[43] Furthermore, it should be noted that Z-scores depend on charts derived from cross-sectional research.[66] Therefore, these Z-scores might not be suitable for longitudinal pediatric studies as this was not their intended use. [66] Berkey and colleagues demonstrated that the use of BMI Z-scores in longitudinal pediatric studies can negatively impact its power and can even complicate the interpretation of results. Therefore, in the study by Berkey *et al.* the change in absolute BMI with incorporation of an age-variable in the statistical model is recommended in longitudinal research in adolescents rather than BMI Z-score[66], which supports the choice for BMI as outcome variable in this review. However, BMI Z-score maintains its value as a cross-sectional parameter incorporating the effects of age and gender to determine the weight category of a child or adolescent at a certain moment in

time. As there is no consensus on which outcome measure to use, Kelly *et al*. advise to report multiple BMI-derived outcome measures opposed to just one in future research, as was done for example in the recently published liraglutide trial where BMI Z-score, absolute BMI and BMI as percentage of the 95th percentile were all reported.[64,67] Thirdly, we have only looked into the effect of weight variability, although many parameters may also experience influence of other factors, for example nutritional habits, physical activity, puberty and ethnicity[52,68,69], as well as other obesity-related comorbidities. For example obstructive sleep apnea and non-alcoholic fatty liver disease might unfavorably alter the cardiometabolic risk profile as well and can be seen as cardiometabolic risk factors themselves.[70,71] However, the complex interplay of these comorbidities, the cardiometabolic risk factors and weight status were not the intended scope of this review. Lastly, weight regain after a weight loss intervention is a negative outcome. Therefore, authors may choose not to report these findings, creating a publication bias in the existing literature and providing an explanation for the low amount of studies eligible for inclusion in this review.

Overall, future researchers should be encouraged to conduct prospective studies with a longer follow-up to determine the longevity of the benefits resulting from the initial weight loss. Secondly, we advise to report the separate risk factors, but also to combine these into one comprehensive endpoint to allow a more definite conclusion on the overall cardiovascular health. As the use of the metabolic syndrome is currently discussed, endothelial function could serve as another surrogate endpoint, combining the influences of all these separate cardiometabolic risk factors.[16,72] Lastly, making a statistical comparison between all the separate timepoints might aid the interpretation of the reader, as this was a

554 difficulty faced when interpreting the results of the currently included studies. Additionally,
555 a comparison with a BMI stable group (as done by Wing *et al.)* or a group that only reduced
556 their BMI without weight regain (as done by Lazzer *et al.)* can provide complementary
557 valuable information[29,73].
558
559 **Conclusion**
560 In conclusion, weight loss can improve the metabolic and cardiovascular profile in children
561 with obesity. In the short term, the benefit of the initial weight loss on the risk factors seems
562 of more importance than the potential weight regain. It seems that the benefit on certain
563 risk factors might be sustained longer than the initial weight loss itself. Nevertheless, caution
564 is warranted with interpretation of these results, since this conclusion is based on a limited
565 number of studies with low sample sizes. Based on the available literature unfortunately, no
566 conclusions can be drawn on the long term cardiometabolic effects of weight regain after
567 weight loss.
568
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574
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Tables

First author (year)	Patient characteristics (n, age, girls, obesity definition)	Design (study type, intervention, follow-up assessments*)	Cardiovascular risk factors studied
Holm *et al.* (2012)	N=115 8-15 years 62 girls, obesity defined based on BMI SDS	Prospective observational study 3-month inpatient weight-reduction program Follow-up at 7, 13 and 25 months after intervention.	Blood pressure
Lausten-Thomsen *et al.* (2015)	Cfr. Study of Holm *et al.*	Cfr. Study of Holm *et al.*	Hs-CRP
Chang *et al.* (2007)	N=49 12-14 years 16 girls BMI ≥95th percentile	Randomized controlled trial 9-month supervised exercise intervention vs control group Follow-up 3 months post-intervention	Fasting glucose and insulin, HOMA-IR Triglycerides Cholesterol (total, HDL and LDL)
Franco *et al.* (2017)	N=22 14-19 years 16 girls BMI≥40 kg/m^2 or ≥35 kg/m^2 with co-morbidities	Retrospective descriptive case series Laparoscopic sleeve gastrectomy Follow-up at 6, 12, 18 and 24 months after surgery	Blood pressure/ hypertension, Fasting glucose and insulin/Insulin resistance/impaired glucose tolerance/ type 2 diabetes Triglycerides Cholesterol (total, HDL and LDL)/dyslipidemia Metabolic syndrome
Sachdev *et al.* (2018)	N=12 Adolescents with tanner stage ≥4 7 girls BMI SDS >3.5	Feasibility study 6 months of intragastric balloon placement as additive to a lifestyle intervention	Blood pressure Fasting glucose and insulin, HOMA-IR, insulin area under the

		Follow-up at 24 months (18 months after balloon removal)	curve following an OGTT Triglycerides Cholesterol (total)
Lazzer *et al.* (2005)	N=26 aged 12-16 years 14 girls BMI>99th percentile for age and gender	Prospective observational study 9 months personalized inpatient weight reduction program Follow-up 4 months after ending the program	Fasting glucose and insulin, Triglycerides Cholesterol (total, HDL and LDL, LDL/HDL ratio)
Shalitin *et al.* (2009)	N=162 aged 6-11 years old with Tanner stage 1 81 girls BMI >95th percentile	Randomized controlled trial 12-week intervention of exercise, diet or both Follow-up 9 months post intervention	Blood pressure CRP and IL-6 Fasting glucose and insulin, HOMA-IR Triglycerides Cholesterol (total, HDL and LDL)
Kelishadi *et al.* (2008)	N=100 aged 7-9 years with Tanner stage 1 number of girls not reported BMI ≥95th percentile	Randomized controlled trial 6-month lifestyle intervention targeted at diet or exercise. Follow-up visit 6 months after ending the intervention	Blood pressure Fasting glucose and insulin, HOMA-IR, QUICKI Triglycerides Cholesterol (total, HDL and LDL)
Okely *et al.* (2010)	N=165 aged 5.5-9.9 years with Tanner stage 1 68 girls BMI defined as overweight or obese by the IOTF criteria but BMI Z-score ≤4.0	Randomized controlled trial 10-weeks face-to-face session followed by 3 monthly relapse-prevention phone calls. The intervention was focused on a parent-centered dietary program, a	Blood pressure Hs-CRP Fasting glucose and insulin Triglycerides Cholesterol (total, HDL and LDL)

				child-centered physical activity program activity or both. Follow-up 6 months after the intervention				

826 *Every study included had assessments at baseline and at the end of the intervention.

827 **Table 1: Overview of study characteristics included in the review**

828

829 **Table 2: overview of the reported results by outcome parameter**

830

	Study (sub)group	**Average weight lost**	**Duration of weight loss**	**Effect of weight loss compared to baseline**	**Average weight regained**	**Duration of weight regain**	**Effect of weight regain compared to nadir weight loss**	**Effect of weight regain compared to baseline**
Waist circumference								
Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	↓	0.5-0.7 kg/m^2	6 months	=	n.r.
Shalitin *et al.*	Overall	1.6 kg/m^2	3 months	↓	1.9 kg/m^2	9 months	↑	↑
Okely *et al.*		0.6 kg/m^2	6 months	↓	0.5 kg/m^2	6 months	n.r.	=
Sachdev *et al.*		2.53 kg/m^2	6 months	↓	5.43 kg/m^2	18 months	n.r.	=
Franco *et al.*		12.3 kg/m^2	12 months	↓	4.7 kg/m^2	12 months	↑	↓
Systolic blood pressure								

Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	↓	0.5-0.7 kg/m^2	6 months	=	n.r.
Shalitin *et al.*	Overall	1.6 kg/m^2	3 months	=	1.9 kg/m^2	9 months	= =	= ↑
	Exercise-only	1.0 kg/m^2		=	1.5 kg/m^2			
Okely *et al.*		0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	=
Holm *et al.*		0.9-1.0 SDS	3 months	↓*	0.6-0.8 SDS	25 months	↑*	↓*
Sachdev *et al.*		2.53 kg/m^2	6 months	=	5.43 kg/m^2	18 months	n.r.	=
Franco *et al.*		12.3 kg/m^2	12 months	↓	4.7 kg/m^2	12 months	↑	n.r.

Diastolic blood pressure

Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	=	0.5-0.7 kg/m^2	6 months	=	n.r.
Shalitin *et al.*		1.6 kg/m^2	3 months	↓	1.9 kg/m^2	9 months	↑	=
Okely *et al.*		0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	=
Holm *et al.*		0.9-1.0 SDS	3 months	↓*	0.6-0.8 SDS	25 months	↑*	↓*
Sachdev *et al.*		2.5 kg/m^2	6 months	=	5.43 kg/m^2	18 months	n.r.	=
Franco *et al.*		12.3 kg/m^2	12 months	=	4.7 kg/m^2	12 months	n.r.	n.r.

Pro-inflammatory profile

Lausten-Thomsen *et al.*	Hs-CRP	0.9-1.0 SDS	3 months	↓*	0.6-0.8 SDS	25 months	↑*	n.r.
Shalitin *et al.*	CRP	1.6 kg/m^2	3 months	=	1.9 kg/m^2	9 months	=	=
	IL-6			=			=	=
Okely *et al.*	Hs-CRP	0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	=
Fasting glucose								
Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	=	0.5-0.7 kg/m^2	6 months	=	n.r.
Shalitin *et al.*		1.6 kg/m^2	3 months	↓	1.9 kg/m^2	9 months	=	=
Okely *et al.*		0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	=
Chang *et al.*		0.6 kg/m^2	9 months	↓	1.2 kg/m^2	3 months	↑	=
Sachdev *et al.*		2.5 kg/m^2	6 months	=	5.43 kg/m^2	18 months	n.r.	=
Lazzer *et al.*	Boys	8.1 kg/m^2	9 months	↓	2.4 kg/m^2	4 months	↑	=*
	Girls	6.3 kg/m^2						
Franco *et al.*		12.3 kg/m^2	12 months	=	4.7 kg/m^2	12 months	=	=
Fasting insulin								
Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	=	0.5-0.7 kg/m^2	6 months	=	n.r.

Shalitin *et al.*		1.6 kg/m^2	3 months	=	1.9 kg/m^2	9 months	↑	↑
Okely *et al.*		0.6 kg/m^2	6 months	↓	0.5 kg/m^2	6 months	n.r.	↓
Chang *et al.*		0.6 kg/m^2	9 months	↓	1.2 kg/m^2	3 months	↑	=
Sachdev *et al.*	Fasting insulin	2.5 kg/m^2	6 months	=	5.43 kg/m^2	18 months	n.r.	=
	Insulin (AUC$^+$ during OGTT$^+$)			↓			n.r.	=
Lazzer *et al.*	Boys	8.1 kg/m^2	9 months	↓	2.4 kg/m^2	4 months	↑	=*
	Girls	6.3 kg/m^2						
Franco *et al.*		12.3 kg/m^2	12 months	↓	4.7 kg/m^2	12 months	=	=

Insulin resistance indices

Kelishadi *et al.*	HOMA-IR	1.04-1.1 kg/m^2	6 months	=	0.5-0.7 kg/m^2	6 months	=	n.r.
	QUICKI			=			=	n.r.
Shalitin *et al.*	HOMA-IR	1.6 kg/m^2	3 months	=	1.9 kg/m^2	9 months	↑	↑
Chang *et al.*	HOMA-IR	0.6 kg/m^2	9 months	↓	1.2 kg/m^2	3 months	↑	=
Sachdev *et al.*	HOMA-IR	2.5 kg/m^2	6 months	=	5.43 kg/m^2	18 months	n.r.	=
Franco *et al.*	HOMA-IR>2.5	12.3 kg/m^2	12 months	↓	4.7 kg/m^2	12 months	n.r.	n.r.

Triglycerides

Kelishadi *et al.*	Diet group	1.1 kg/m^2	6 months	↓	0.7 kg/m^2	6 months	=	n.r.
	Exercise group	1.04 kg/m^2		=	0.5 kg/m^2		=	n.r.
Shalitin *et al.*		1.6 kg/m^2	3 months	↓	1.9 kg/m^2	9 months	↑	=
Okely *et al.*		0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	=
Chang *et al.*		0.6 kg/m^2	9 months	↓	1.2 kg/m^2	3 months	↑	=
Sachdev *et al.*		2.5 kg/m^2	6 months	=	5.43 kg/m^2	18 months	n.r.	=
Lazzer *et al.*	Boys	8.1 kg/m^2	9 months	↓	2.4 kg/m^2	4 months	↑	↓*
	Girls	6.3 kg/m^2						
Franco *et al.*		12.3 kg/m^2	12 months	↓	4.7 kg/m^2	12 months	n.r.	n.r.

LDL cholesterol

Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	=	0.5-0.7 kg/m^2	6 months	=	n.r.
Shalitin *et al.*		1.6 kg/m^2	3 months	=	1.9 kg/m^2	9 months	=	↓
Okely *et al.*		0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	↑
Chang *et al.*		0.6 kg/m^2	9 months	=	1.2 kg/m^2	3 months	=	=

Lazzer *et al.*	Boys	8.1 kg/m^2	9 months	↓	2.4 kg/m^2	4 months	↑	=*
	Girls	6.3 kg/m^2						
Franco *et al.*		12.3 kg/m^2	12 months	=	4.7 kg/m^2	12 months	n.r.	n.r.

HDL cholesterol

Kelishadi *et al.*		1.04-1.1 kg/m^2	6 months	=	0.5-0.7 kg/m^2	6 months	=	n.r.
Shalitin *et al.*		1.6 kg/m^2	3 months	↓	1.9 kg/m^2	9 months	↑	=
Okely *et al.*		0.6 kg/m^2	6 months	=	0.5 kg/m^2	6 months	n.r.	=
Chang *et al.*		0.6 kg/m^2	9 months	=	1.2 kg/m^2	3 months	↑*	↑*
Lazzer *et al.*	Boys	8.1 kg/m^2	9 months	=	2.4 kg/m^2	4 months	↑	n.r.
	Girls	6.3 kg/m^2						
Franco *et al.*		12.3 kg/m^2	12 months	↑	4.7 kg/m^2	12 months	↑	↑

831 = : no significant difference

832 ↓: significantly decreased ($p<0.05$)

833 ↑: significantly increased ($p<0.05$)

834 n.r.: not reported: data are presented, but statistical comparison was not performed.

835 * reported to change, but no p-value was provided by the authors

836 +: AUC is area under the curve, OGTT is oral glucose tolerance test