The Association of Weight Loss and Cardiometabolic Outcomes in Obese Children: Systematic Review and Meta-regression


Background: Excess body weight in children is associated with multiple immediate and long-term medical comorbidities. We aimed to identify the degree of reduction in excess body weight associated with cardiometabolic changes (lipid panel, liver function tests, systolic blood pressure (SBP), diastolic blood pressure, glycosylated hemoglobin, and fasting blood glucose) in overweight and obese children.

Methods: We conducted a comprehensive search of MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Scopus through February 12, 2015. We included randomized controlled trials and cohort studies that evaluated interventions to treat pediatric obesity (medication, surgery, lifestyle, and community-based interventions) with ≥ a 6-month follow-up. We used a random effects meta-regression approach to assess the association between body mass index (BMI)/weight and cardiometabolic changes.

Results: We included 42 studies (37 randomized controlled trials and five cohorts) enrolling 3807 children (mean age, 12.2 years; weight, 74.7 kg; and BMI, 31.7 kg/m²). Studies had overall moderate to low risk of bias. A 1-mm Hg decrease in SBP was significantly associated with a decrease of 0.16 kg/m² (P = .04) in BMI. A 1-mg/dL increase in HDL was significantly associated with a 0.74-kg decrease in weight (P = .02). A 1-mg/dL decrease in triglycerides was significantly associated with a 0.1-kg decrease in weight (P = .03). The remaining associations were not statistically significant.

Conclusions: Weight reduction in children is associated with significant changes in several cardiometabolic outcomes, particularly HDL, SBP, and triglycerides. The magnitude of improvement may help in setting expectations and may inform shared decision-making and counseling. (J Clin Endocrinol Metab 102: 758–762, 2017)
adults were overweight as children, and two-thirds of children with childhood obesity with the highest BMI quartile became young adults with the highest BMI (3–5). Consequently, typically adult metabolic disorders related to obesity, like hypertension, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome, are becoming increasingly prevalent among children and adolescents (6–9), underscoring the need for early surveillance and detection programs.

Several types of interventions, including lifestyle modifications, medications, surgery, and community-based interventions, have been implemented to tackle the excess body weight in children. Although several studies have shown improvement in the metabolic outcomes along with weight loss in children, it is always challenging to determine the magnitude of weight loss to recommend to children and their parents. It is also unclear which BMI level to target in children. BMI has high specificity but low sensitivity to detect excess adiposity and fails to identify over one-fourth of the children with excess body fat percentage (10). Therefore, there is a need to measure the degree of change in cardiometabolic outcomes (lipid panel, liver function tests, systolic blood pressure [SBP], diastolic blood pressure [DBP], glycosylated hemoglobin, and fasting blood glucose) that is associated with a particular change in body weight or BMI (11, 12).

A task force from the Endocrine Society was charged with developing guidelines for the management of pediatric obesity. To aid in the development of these recommendations, we performed a systematic review of the literature and a meta-regression analysis to determine how weight loss achieved in children translates into favorable outcomes. This knowledge may also help in counseling and motivating children and their families about maintaining a healthy weight.

Materials and Methods

Considering the availability of many childhood obesity intervention studies as well as multiple well-conducted systematic reviews of these studies, we followed an “umbrella” approach (systematic review of systematic reviews) (13, 14) to identify eligible randomized controlled trial (RCTs) and cohort studies that compared weight loss interventions to placebo or usual care in children. We followed a predefined protocol developed by a task force from the Endocrine Society to conduct this systematic review. We followed the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (15).

Eligibility criteria for individual studies

We included RCTs and cohort studies that enrolled overweight and obese children (defined as ≥ 85th percentile BMI) between 2 and 18 years of age and evaluated interventions to treat pediatric obesity (medications, surgery, lifestyle interventions, and community-based interventions). Both English and non-English language studies were included. We excluded studies with < 6-month follow-up duration and studies that did not report both weight outcome changes and metabolic outcome changes.

Outcomes

Body weight outcomes included changes in BMI (absolute, percentage, percentile, or z-score change) and changes in weight (absolute, percentage, or percentile change). Metabolic outcomes included changes in glycosylated hemoglobin, fasting blood glucose (FBG), 2-hour oral glucose tolerance test, SBP and DBP, lipids panel (total cholesterol, low-density lipoprotein, high-density lipoprotein [HDL], and triglyceride [TG]), and liver function tests (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase).

Search strategy

A comprehensive search of several databases, in any language and from the inception of each database to February 12, 2015, was conducted. The databases included Medline In-Process and Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study’s principal investigator. Controlled vocabulary supplemented with keywords was used to search for systematic reviews and meta-analyses of interventions for pediatric obesity. Supplemental Table 1 describes the detailed search strategy.

Data synthesis

Search output was uploaded into an online reference management system (DistillerSR) to allow fast and transparent processing with better tracking and real-time evaluation of interreviewer agreement and progress of reviewers.

Identifying systematic reviews

Two reviewers independently screened abstracts for eligible systematic reviews. They retrieved and independently screened full-text manuscripts. Conflicts were resolved by a third reviewer. We selected the most recent systematic review and, if more than one was available, selected the most comprehensive one using a tool for evaluating the credibility of systematic reviews (Assessment of Multiple Systematic Reviews) (16, 17). We included at least one systematic review per intervention.

Identifying individual studies

We retrieved the full-text manuscripts of the studies included in the systematic reviews. Two independent reviewers screened full-text manuscripts for eligibility criteria. Data extracted were descriptions of participants, details of interventions, and measures of outcomes of interest. We contacted authors of seven studies for missing or incomplete data or more baseline data. However, in most cases, data weren’t available or authors failed to respond.

Assessment of the risk of bias of individual studies

We used the Cochrane risk of bias tool and the Newcastle-Ottawa Scale to assess the methodological quality of included RCTs and cohort studies, respectively.
Statistical analysis

We used a random-effects regression model with the heterogeneity estimated from the Mantel-Haenszel model to assess the association between BMI or weight changes and metabolic changes. All analyses were conducted using STATA, version 13 (StataCorp LP). The quality of evidence (ie, certainty in estimates) was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (18, 19) approach.

Results

Search results and study description

A total of 1245 systematic reviews were identified by the electronic search strategy, of which 388 were eligible for full-text screening. Forty-five systematic reviews were finally eligible for individual study selection, which yielded 37 RCTs and five cohort studies enrolling 3807 patients (mean age, 12.2 years; weight, 74.7 kg; and BMI, 31.7 kg/m²). The screening process is represented in Figure 1. The length of follow-up ranged from 6 to 24 months. The characteristics of the included studies are summarized in Supplemental Table 2.

Meta-regression results

Estimated metabolic change per weight and BMI change are summarized in Table 1 along with median (interquartile range) within which these associations were tested. For the studied sample with baseline median BMI of 30 kg/m² (26.1, 35.47) and median weight of 70.1 kg (53.5, 89.1), a 1-unit (mm Hg) decrease in SBP was associated with a BMI decrease of 0.16 kg/m² and a body weight decrease of 0.61 kg. Changes in body weight measures associated with a change in DBP, however, were not statistically significant. In terms of serum lipids, a 1-mg/dL increase in HDL was associated with a 0.74-kg decrease in body weight (P = .02) for subjects with a baseline median body weight of 62.5 kg (52.05, 89.5), whereas a 1-mg/dL decrease in TGs was associated with a 0.1-kg decrease in body weight for subjects with baseline median body weight of 70.1 kg (56.4, 87.5).

Data on the metabolic outcomes of liver enzymes and glycosylated hemoglobin were unavailable to allow quantitative assessment of the association with a change in weight and BMI.

Heterogeneity and subgroup analyses

As shown in Supplemental Tables 3–7, heterogeneity was further explored by conducting subgroup analyses based on study design (RCT vs cohort), type of intervention (exercise-based, diet-based, mixed lifestyle interventions, and medication), length of follow-up (<1 year and ≥1 year), and age (younger vs older, using two cutoffs of 10 and 12 years). The only significant interaction suggested that longer follow-up > 12 months is associated with more change in BMI per 1-unit change in FBG and HDL. No significant interaction was detected for other subgroups, whereas some comparisons were not feasible due to the low number of included studies in that subgroup.

Quality of evidence

Overall, studies had a moderate to low risk of bias. The quality of evidence (ie, certainty in estimates) was low due to the observational nature of the tested associations and high heterogeneity.

Discussion

Some experts believe that the weight-focus approach is not effective in achieving a sustained favorable effect on patients’ metabolic outcomes (20). The focus of this study, however, was on cardiometabolic changes as the end outcome. Multiple studies have shown an association between weight loss and significant improvements in metabolic indicators like blood pressure and serum lipids in obese children (21–24); we aimed to evaluate the degree of such improvements in metabolic outcomes that is associated with weight reduction, regardless of the method used to achieve the change in weight. Due to the young age of patients and the relatively short follow-up period (6 to 24 months) in all the included studies, it was not feasible to accurately evaluate the long-term patient-important outcomes, such as mortality and subsequent development of diabetes (25). However, we found that even a minimal reduction in BMI might lead to clinically significant improvement in some metabolic outcomes. For instance, a 0.16-kg/m² decrease in BMI was associated with 1 mm Hg improvement in SBP. Assuming a linear correlation between SBP change and BMI reduction, a reduction of SBP by 10 mm Hg may require a reduction of

Figure 1. The process of study selection.
BMI by 1.6 kg/m². This same reduction in BMI is associated with a 16-mg/dL reduction in TG and a 1.7-mg/dL increase in HDL. In subgroup analysis, we note that longer follow-up (>12 months) was associated with more BMI change per 1-unit change of HDL and FBG. This may be interpreted to suggest that the same changes in FBG and HDL levels were harder to achieve beyond 12 months of follow-up and required more weight reduction. However, weight loss per se also becomes harder with longer follow-up. Many patients attempting weight loss tend to regain some of their lost weight after the first year, and only about 20% of people in the general population are successful at long-term weight loss maintenance (26, 27). The clinical implications of the current analysis may be viewed from a public health perspective, although we see results most relevant to the patient-physician dyad. Shared decision-making occurring when physicians engage children and their families can be better informed by information from this systematic review. Expectations about metabolic changes and blood pressure improvement associated with weight or adiposity reduction can be quantitatively framed during such discussions. Our data can be used for counseling adolescent boys or girls and their parents about weight loss that is needed to correct abnormal blood pressure and serum lipids. A clinician can inform them that losing 1 kilogram is expected to be associated with a reduction in serum TGs of 5 mg/dL and an increase in HDL-cholesterol of approximately 1.5 mg/dL. Reducing the BMI in the adolescent boy or girl by 1 unit is expected to reduce SBP by approximately 6 mm Hg.

### Limitations and strengths

Inferences from this analysis are limited by reporting bias. It is plausible that other studies have measured metabolic changes and weight/BMI but did not publish or report such association. The quality of the evidence is clearly limited by the observational nature of the associations being tested and by heterogeneity. Associations observed using aggregate data across studies are subject to the ecological fallacy. Therefore, associations not found to be statistically significant in this meta-regression may in fact be true if tested in future, larger, and more rigorous randomized trials that aim to answer the question of association. Furthermore, the associations noted in this analysis may only hold true in patients within the age and weight parameters of patients enrolled in the included studies (ie, markedly obese adolescents). The strengths of this systematic review relate to following a priori established protocol, selecting and appraising studies by pairs of independent reviewers, the comprehensive nature of the search spanning multiple databases, and the multidisciplinary nature of the research team that included expert input from the Endocrine Society as well as expertise in preventive medicine and public health, clinical epidemiology, statistics, and library science.

### Conclusion

Weight reduction in children is associated with significant changes in several cardiometabolic outcomes, particularly HDL, SBP and TGs. The magnitude of improvement may help in setting expectations and inform shared decision making and counseling.

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References