Study protocol

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Effects of multicomponent interventions on biochemical markers in obese youth: a systematic review protocol

Efeitos de intervenções multicomponentes em marcadores bioquímicos em jovens obesos: um protocolo de revisão sistemática

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ABSTRACT

Physical exercise is effective in modulating circulating inflammatory markers of obesity. However, little is known about the effects of interventions with physical exercise programs accompanied by nutritional and/or psychological guidance, configuring themselves as multicomponent programs. Thus, the aim of this review is to systematically evaluate the evidence related to the effects of multicomponent weight-loss interventions in modulating circulating inflammatory markers in children and adolescents. Therefore, the following databases will be searched to identify all relevant articles: PubMed, SciELO, Lilacs, Web of Science, EMBASE, Scopus, SPORT Discus. Randomized controlled trials and quasi-experimental studies of children and adolescents (6 to 18 years old) will be included. Eligible interventions will target weight-related behaviors (including diet, physical activity, behavior modification and/or combinations thereof). Two independent reviewers will select studies using Rayyan QCRI software and extract the data to a standard form. The main outcomes of the review will be the circulating values of leptin, interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF- α) in a quantitative way. To assess the methodological quality (or risk of bias) of individual studies, Effective Public Health Practice Project assessment tool will be used. The meta-analysis will be performed using the Review Manager software.

Keywords: Obesity; Excess weight; Biochemical markers; Youths.

RESUMO

O exercício físico é eficaz na modulação dos marcadores inflamatórios circulantes da obesidade. Porém, pouco se sabe sobre os efeitos de intervenções com programas de exercícios físicos acompanhados de orientações nutricionais e/ou psicológicas, configurando-se como programas multicomponentes. Assim, o objetivo deste protocolo é propor uma revisão sistematicamente das evidências relacionadas aos efeitos de intervenções multicomponentes para perda de peso na modulação de marcadores inflamatórios circulantes em crianças e adolescentes. Para tanto, as seguintes bases de dados serão pesquisadas para identificar todos os artigos relevantes: PubMed, SciELO, Lilacs, Web of Science, EMBASE, Scopus, SPORT Discus. Serão incluídos ensaios clínicos randomizados e estudos quase experimentais com crianças e adolescentes (6 a 18 anos). As intervenções elegíveis terão como foco a melhora dos comportamentos relacionados ao peso (incluindo dieta, atividade física, modificação de comportamento e/ou combinações dos mesmos). Dois revisores independentes selecionarão estudos usando o software Rayyan QCRI e extrairão os dados em um formulário padrão. O principal resultado da revisão serão os valores circulantes de leptina, interleucina 6 (IL-6) e fator de necrose tumoral alfa (TNF-α) de forma quantitativa. Para avaliar a qualidade metodológica (ou risco de viés) de estudos individuais será utilizada a ferramenta de avaliação Effective Public Health Practice Project. A meta-análise será realizada no software Review Manager.

Palavras-chave: *Obesidade; Excesso de peso; Marcadores bioquímicos; Jovens.*

Introduction

The prevalence of excess weight (overweight and obesity) in childhood has increased worldwide, constituting a serious public health problem that led to economic consequences and high health costs[1,2]. Further, excess body fat can result in increased secretion of pro-inflammatory markers causing a chronic state of low-grade systemic inflammation. This state contributes to the development of processes related to insulin resistance, type 2 diabetes mellitus, visceral obesity, and metabolic syndrome[3,4].

In addition, physical inactivity and sedentary behavior, which are increasingly present in the modern lifestyle, are directly linked with increasing obesity prevalence and incidence among childhood and youth, which in turn is associated with increasing comorbidities that may arise throughout life, such as hypertension, insulin resistance, diabetes mellitus, sleep apnea, and cardiovascular disease[5,6].

Furthermore, in times of social distance due to the pandemic of COVID-19 that we are living in, there is a significant change in the routine of young people, making it possible to increase stress and the development of obesity that proposes an increase in inflammation and immune response[7]. Therefore, it is crucial to efficiently intervene in order to decrease overweight and obesity prevalence and its metabolic complicatons[8].

Nowadays, physical exercise has been recognized as a mechanism capable of promoting a protective impact associated with the modulation of inflammatory processes and the consequent reduction in the risk of chronic cardiovascular and metabolic diseases[9–12]. Previous data reported on the effect of physical exercise on children and adolescents has shown the ability to diminish pro-inflammatory cytokines[13-19]. However, other studies have suggested that although physical exercise contributes to improving body composition, it does not appear to significantly modify the levels of inflammatory cytokines in overweight or obese children and/or adolescents[20,21].

A meta-analysis of intervention with physical activity in obese or overweight children and adolescents suggested that there was no significant association between physical activity and interleukin 6 (IL-6) or/and tumor necrosis factor-alpha (TNF-α), however, there was a tendency to decrease IL-6[8]. Thus, although there are already systematic reviews that describe the role of physical activity/exercise in influencing the levels of inflammatory cytokines in children and adolescents with overweight or obesity[8,18,21], these separately analyze interventions with physical exercise programs without considering other components that may be of critical importance to change the lifestyle of this population, such as nutritional monitoring and psychological support. Therefore, this research is relevant since the treatment for excess weight must consider the individual and social aspects, enabling the adaptation of a healthier lifestyle and the maintenance of this after the intervention program[23,24].

Thus, this systematic review study with meta-analysis is justified in order to meet the following objectives (1): analyze the available literature regarding the chronic effects of multicomponent interventions on circulating levels of leptin, IL-6, and TNF-α in children and adolescents overweight or obese; (2): describe which are the most frequent components in interventions for the treatment of overweight and (3): compare the chronic effects of multicomponent interventions on the analyzed variables, stratifying by sex, sexual maturation and degree of obesity.

Methods

- **Study Registration**

This systematic review protocol followed the guidelines indicated in Preferred Reported Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P, 2015)[25]. We provide the PRISMA checklist in Additional file 1. In addition, this protocol is under review in the Prospective International Registry of Systematic Reviews (PROSPERO) (registration number: CRD42020196556; date of registration: August 1, 2020).

- **Inclusion criteria for study selection**

Studies will be selected according to the criteria outlined in Table 1.

- **Types of studies**

We will include randomized controlled trial (RCT) and controlled (non-randomized) clinical trial (CCT).

- **Participants**

Studies that examined the pediatric population aged 6 to 18 years old who, before the intervention program, presented excess of weight (overweight or obesity) will be included. This approach is justified by the importance of researching the effects of interventions in young populations.

- **Types of interventions**

Lifestyle interventions and reduction of body weight with a period ≥ 12 weeks in duration, with programs

Table 1 – Inclusion and exclusion criteria

PICOS strategy	Inclusion criteria	Exclusion criteria
P - Population	Children and adolescents aged between 6 and 18 years classified with overweight or obesity by body mass index values.	Children and adolescents that presented comorbidity/disease associated with obesity.
I – Intervention	Lifestyle interventions carried out in specific schools, clinics, or institutions, lasting ≥12 weeks and these programs being composed of more than one intervention component (one that used programmed physical exercise (e.g., sports, resistance training, aerobic training, etc), which was associated with nutritional or psychological guidance or even containing the three components). Studies with totally theoretical or educational interventions without practical interventions will not be accepted.	Interventions with complementary/alternative treatments, dietary supplements intended for weight loss.
C – Comparison	Group of overweight or obese children and adolescents who did not participate in any type of intervention or guidance.	
O – Outcome	Inflammatory markers (Leptin, IL-6, TNF-α).	Studies that evaluated the acute effects of the intervention.
S – Study design	Intervention studies (e.g., RCT, Non-controlled trials).	Observational studies, (cross sectional, case-control, and cohort studies), reviews, case reports, case series, in vitro studies, animal studies, secondary analyses of trials, and survey development studies.

IL-6 = Interleukin 6; TNF-α = Tumor necrosis factor-alpha; RCT = Randomized Controlled Trial

composed of more than one intervention component, having these, essentially held sessions with programmed physical exercises associated with another component such as diet/nutritional or psychological counseling or even combining all components.

Programs should have the physical activity component or regular, targeted physical exercise (for example, guidelines for increasing leisure time, reducing sedentary behavior). In addition to the exercise program, studies must have at least one more intervention component, such as nutritional diet or psychological assistance. Dietary interventions are defined as those in which the subject's diet is modified through changes in eating-related behaviors (e.g., portion control, food substitutions, and cooking skills). Psychological guidelines may refer to stimulus control programs, psychoeducation, cognitive-behavioral guidelines (for example, anxiety control using cognitive and relaxation techniques).

- **Comparators**

The reference group will include children and adolescents with overweight or obesity who did not participate in any type of intervention or guidance during the period in which the study was developed.

- **Types of outcomes**

The studies to be included in this review must report, as a primary or secondary result, the circulating values of at least one of the following variables: leptin, IL-6, TNF-α, in a quantitative way, regardless of the analysis and the measurement unit used for assessment.

- **Search methods for identification of studies**

A comprehensive search of seven electronic databases will be performed including PubMed, SciELO, Lilacs, Web of Science, EMBASE, Scopus, SPORTDiscus from setup time to 31th March 2021. The survey will be complemented with suggestions from experts in the field.

The chosen keywords will be identified by "quotes" and duly separated by the Boolean terms AND and OR. Combinations of free words and subject terms will be used to search, which will not be limited by language. Similarly, cross-search will be carried out in all databases to ensure that all relevant articles are identified. An example of a search strategy for the PubMed database is shown in Additional file 2.

- **Data collection and analysis**
- *Selection of studies*

Search results in electronic databases will be loaded by XX into the EndNote Web quote manager and the duplicates will be removed. Then, the EndNote Web file will be loaded into the Rayyan QCRI software in which XX and XXX will independently start the study selection process. The selection of studies will take place in three phases: a) exclusion of duplicates within and

between databases; b) selection of articles by reading the title and abstracts, and at this stage, the summary of articles must meet most of the eligibility criteria to be selected for reading in full; c) selection of articles by reading them in full. At this stage, articles must meet all the eligibility criteria to be included in the present study. The three phases will be carried out by two independent reviewers and the reasons for the exclusion of unselected materials should be recorded. When two or more studies describe a single trial, only one publication from that research project will be included. In case of doubts or disagreements between reviewers, the inclusion or exclusion of the study will be decided by discussion and a third researcher (XXX) will assist in the evaluation in cases of disagreement.

• *Data extraction and management*

The data in these articles will be extracted independently by XX and XXX and reviewed by XXX. If data extraction from a selected study cannot be performed due to the lack of information or information inadequately described in the full-text article, XX will contact the corresponding author of the publication by e-mail to request that information.

A standard form will be used to record the following data:

- Author(s) and year of publication;
- City and country where the study was conducted;
- Year of data collection;
- Info about participating population (age, sex and race/ethnicity) and its nutritional status;
- Study design (randomized; non-randomized or quasi-experimental trial);
- Characteristics of the intervention (duration, components used in the program, exercise/diet / psychological orientation, etc.);
- Comparator and description;
- Outcome information (baseline and after intervention of circulating levels of leptin, IL-6 and TNF-α);
- Information on secondary results (change in body weight, nutrition, psychological behavior, level of physical activity, or improvement in physical fitness).

• *Quality of included studies*

Methodological quality of included studies will be assessed using a 20-item checklist developed from the Effective Public Health Practice Project (EPHPP)[26], which include important domains of trials:

- Selection (e.g., if the individuals selected to participate in the study likely to be representative of the target population and percentage of selected individuals agreed to participate);
- Study design (e.g., if there is a control group, whether the allocation of groups was randomized);
- Control of confounding factors (e.g., in regard of possible differences between groups prior to the intervention and whether there was adjustment of variables in the analyses);
- Blinding of outcome assessor;
- Data collection methods (e.g., use of validated and reproducible instruments);
- Withdrawals and dropouts in follow-up (e.g., whether there is a description of losses along follow-up, considering ≥20% with moderate risk of bias and ≥50% high risk of bias for this domain);
- Intervention integrity (e.g., whether there were any adjustments to the protocol and whether there was a risk of contamination) and
- Analyses (e.g., whether the techniques used are appropriate and whether there was an intention-to-treat approach)

Two reviewers (XX and XXX) will categorize each trial as low, moderate or high quality. A third reviewer (XXX) will assist in resolving disagreements.

• *Measures of treatment effect*

The statistical analysis will be performed in the RevMan Software (version 5.3 for Windows; Nordic Cochrane Center, Copenhagen, Denmark). The forest graphics will be used to illustrate the strength of the healing effects. The continuous outcomes analyzed will be through mean and standard deviation. The measure of standardized means with a random effect will be adopted, in view of obtaining different measurement units between studies.

• *Missing data*

The corresponding author will be contacted to obtain missing data. If the missing data cannot be obtained within a 15-day period, the study will be deleted.

• *Assessment of heterogeneity*

To verify the heterogeneity between the included studies, it will be the χ^2 test (test level a = 0.1) and the I^2 statistic was used[27]. The fixed or random effect models

will be determined depending on the I^2 statistic. Subgroup analyzes will be carried out observing the comparison between randomized and non-randomized clinical studies, sex, nutritional status, sexual maturation, and duration of the intervention program.

- *Assessment of reporting biases*

Funnel charts will be used to illustrate publication bias when 10 or more studies are included in the meta-analysis. To assess the risk of bias in non-randomized studies, the ROBINS-I tool will be used[28].

- *Data synthesis*

RevMan software (v.5.3) will be used to calculate the relative risk (RR) in dichotomous data and the mean difference (MD) for variables with continuous data. The estimated value and the 95% CI of each effect will be calculated. If the research results are not significantly different (I^2 < 50%), a fixed-effect model will be used for the meta-analysis. In addition, if the search results are significantly different (I^2 > 50%), a meta-analysis will be performed using a random-effects model after further analysis of the heterogeneity of sources.

The textual review will be used to summarize the conclusions of the included studies if the data are not adequate to match quantitatively. In trials that report only pre- and post-intervention values, the mean changes will be obtained by subtracting the pre-measurements of post-measurements and the standard deviation (SD) will be calculated for these changes.

- *Subgroup analysis*

Subgroup analyzes will be carried out observing the comparison between randomized and non-randomized clinical studies, sex, degree of overweight, sexual maturation, and the duration of the intervention program.

Discussion

This is a systematic review protocol that aims to assess the chronic effects of multicomponent interventions on circulating leptin, IL-6 and TNF-α levels in overweight or obese children and adolescents, as well as to describe which are the most frequent components in interventions to treat weight excess; to compare the chronic effects of multicomponent interventions on the analyzed variables stratifying by sex, sexual maturation and degree of obesity.

Identifying the biochemical results of interventions conducted over 12 weeks and that include more components for the treatment of overweight in children and adolescents is important to contribute to the development of future interventions in this population. Furthermore, obesity is associated with low-grade inflammation and changes in adipose tissue that promote increased tissue quality, instead of quantity, can modify adipokine level and signaling[20]. In addition, identifying more efficient methods for reducing these adipokines may be relevant to prevent chronic diseases associated with obesity in the long term. Thus, it is necessary to highlight the importance of interventions that propose programs aimed at the global development of the individual with a multicomponent and multi-professional approach in the treatment of factors that contribute to the development of obesity, enabling the lifestyle to remain healthy even after treatment[23,24].

In light of these relationships that permeate the emergence of obesity reflecting chronic inflammation and metabolic disease, it is important to think of valid methods to control childhood obesity and prevent diseases in adulthood[30]. Thus, the results of this study can assist in structuring more specific and efficient public policies focused on this population.

An initial search was carried out in order to understand which were the primary studies and to identify potential limitations that include studies with small samples, insufficient details of eligibility and/or sample intervention, strategies and characteristics. In addition, differences in treatment programs for overweight children and adolescents in the included studies can result in heterogeneity. The changes made to this protocol during the course of the study will be described in PROSPERO and outlined in the final manuscript published later. The findings of this review will be disseminated in conference presentations and peer-reviewed publications.

Conflict of interest

The authors declare no conflict of interest.

Author's contributions

Borfe L, Guerra PH, Gaya AR participated in the initial study design. Borfe L, Guerra PH, Brazo-Sayavera J and Gil JFL wrote the text. Guerra PH, Reuter CP, Brand C and Gaya AR were responsible for supervising and critically reviewing the content.

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Attachments

Additional file 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item Nº	Checklist item	(Page Nº#)
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	5
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	5
Support			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2, 3
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	2, 3, 4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	2, 3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Additional File 2
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	3, 4, 5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	3, 4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	4, 5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available)

for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.
From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Additional file 2. PubMed Search Strategy (24/01/2021).

A comprehensive search of 7 electronic databases will be carried out, including PubMed, SciELO, Lilacs, Web of Science, EMBASE, Scopus, SPORTDiscus, and the search for keywords in the titles and abstracts of the studies will be carried out.

Borfe L, PubMed Search Strategy (24/01/2021)

- **CHILD OR ADOLESCENT**

"Child"[Mesh] OR "Adolescent"[Mesh]
OR "Child" OR "Children" OR "Adolescent"[Mesh] OR "Adolescent" OR "Adolescents" OR "Adolescence" OR "Teens" OR "Teen" OR "Teenagers" OR "Teenager" OR "Youth" OR "Youths" OR "Adolescents, Female" OR "Adolescent, Female" OR "Female Adolescent" OR "Female Adolescents" OR "Adolescents, Male" OR "Adolescent, Male" OR "Male Adolescent" OR "Male Adolescents"

- **OBESITY**

"Obesity"[Mesh]
OR "Obesity"[Mesh] OR "Obesity" OR "Overweight"[Mesh] OR "Overweight"

- **EXERCISE**

"Exercise"[Mesh]
OR "Exercise" OR "Exercises" OR "Physical Activity" OR "Activities, Physical" OR "Activity, Physical" OR "Physical Activities" OR "Exercise, Physical" OR "Exercises, Physical" OR "Physical Exercise" OR "Physical Exercises" OR "Exercise, Aerobic" OR "Aerobic Exercise" OR "Aerobic Exercises" OR "Exercises, Aerobic" OR "Exercise Training" OR "Exercise Trainings" OR "Training, Exercise" OR "Sport" OR "Multicomponent intervention" OR "multicomponent intervention"

- **INFLAMMATORY MARKERS**

"Leptin"[Mesh]
OR "Leptin" OR "Obese Protein" OR "Obese Gene Product" OR "Ob Gene Product" OR "Ob Protein" OR "Interleukins"[Mesh] OR "Interleukins" OR "Interleukin" OR "Tumor Necrosis Factor-alpha"[Mesh] OR "Tumor Necrosis Factor alpha" OR "Tumor Necrosis Factor" OR "TNFalpha" OR "TNF-alpha" OR "TNF" OR "Inflammatory Markers"

- **FINAL SEARCH (combining above listed search sets):**

CHILD OR ADOLESCENT AND OBESITY AND EXERCISE AND INFLAMMATORY MARKERS