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The influence of physical activity and vitamin D on serum levels of interleukin-10 in children and adolescents. Protocol of systematic review

A influência da atividade física e vitamina D e níveis séricos de interleucina-10 em crianças e adolescentes. Protocolo de revisão sistemática

La influencia de la actividad física y los niveles de vitamina D e interleucina-10 sérica en niños y adolescentes. Protocolo de revisión sistemática

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Abstract
Recent studies indicate a great relationship between the combination of physical activity, levels of vitamin D and interleukin-10, these factors are interpreted as indicators of health from children to adolescents. Therefore, the proposal of the protocol was to describe the aims and methods for a systematic review to summarize the studies by examining the influence of physical activity and vitamin D on serum levels of interleukin-10 in children and adolescents. A systematic review will be developed based on searches of articles in seven electronic databases and references of retrieved articles, contact with authors, and study repositories. Eligibility criteria: observational or experimental studies examining the Influence of Physical Activity and Vitamin D on Serum Levels of Interleukin-10 in Children and Adolescents (9 to 13y). Selection of the studies and extraction of the data will be carried out by two reviewers independently. Characteristics of the study, participants, methods of combinations, and main results will be extracted and described. Risk of bias and level of evidence in the studies will be assessed according to the Cochrane handbook The data will be synthesized using random effects meta-analysis for results that are homogeneous in terms of statistical, clinical, and methodological characteristics. If not, then a narrative synthesis will be conducted. The results of this review may provide insights to improve the current influence of physical activity and vitamin D on serum levels of interleukin-10 in children and adolescents, as well as a guide to future studies in this research field.
Keywords: Exercise; Vitamin D; Interleukin-10; Child; Adolescent.

Resumo

Estudos recentes indicam uma relação grandiosa entre a combinação de atividade física, os níveis de vitamina D e interleucina-10, esses fatores são interpretados como indicadores de saúde de crianças de adolescentes. Portanto, a proposta deste protocolo é descrever os objetivos e métodos para uma revisão sistemática para resumir os estudos que examinaram a influência da atividade física e da vitamina D nos níveis séricos de interleucina -10 em crianças e adolescentes. Uma revisão sistemática será desenvolvida com base em buscas de artigos em sete bases de dados eletrônicas e referências de artigos recuperados, contato com autores e repositórios de estudo. Critérios de elegibilidade: estudos observacionais ou experimentais que examinam a influência da atividade física e da vitamina D e os níveis séricos de interleucina -10 em crianças e adolescentes (9 a 13 anos). A seleção dos estudos e a extração dos dados serão realizadas por dois revisores de forma independente. Características do estudo, participantes, métodos de combinações e principais resultados serão extraídos e descritos. O risco de viés e o nível de evidência dos estudos serão avaliados de acordo com o manual Cochrane. Os dados serão sintetizados por meio de metanálise de efeitos aleatórios para resultados suficientemente homogêneos em termos de características estatísticas, clínicas e metodológicas. Caso contrário, será realizada uma síntese narrativa. Os resultados desta revisão podem fornecer subsídios para melhorar a atual influência da atividade física e da vitamina D nos níveis séricos de interleucina-10 em crianças e adolescentes, bem como orientar estudos futuros neste campo de pesquisa.
Palavras-chave: Exercício físico; Vitamina D; Interleucina-10; Criança; Adolescente.

Resumen

Estudios recientes indican una gran relación entre la combinación de actividad física, niveles de vitamina D e interleucina-10, estos factores son interpretados como indicadores de salud en niños y adolescentes. Por lo tanto, el propósito de este protocolo es describir los objetivos y métodos de una revisión sistemática para resumir los estudios que examinaron la influencia de la actividad física y la vitamina D en los niveles séricos de interleucina -10 en niños y adolescentes. Se desarrollará una revisión sistemática basada en búsquedas de artículos en siete bases de datos electrónicas y referencias de artículos recuperados, contacto con autores y repositorios de estudios. Criterios de elegibilidad: estudios observacionales o experimentales que examinen la influencia de la actividad física y la vitamina D y los niveles séricos de interleucina -10 en niños y adolescentes (de 9 a 13 años). Dos revisores de forma independiente realizarán la selección de estudios y la extracción de datos. Se extraerán y describirán las características del estudio, los participantes, los métodos de combinación y los principales resultados. El riesgo de sesgo y el nivel de evidencia de los estudios se evaluarán según el manual Cochrane. Los datos se sintetizarán mediante metanálisis de efectos aleatorios para obtener resultados suficientemente homogéneos en cuanto a características estadísticas, clínicas y metodológicas. En caso contrario, se realizará una síntesis narrativa. Los resultados de esta revisión pueden proporcionar subsidios para mejorar la influencia actual de la actividad física y la vitamina D en los niveles séricos de interleucina-10 en niños y adolescentes, así como orientar futuros estudios en este campo de investigación.
Palabras clave: Ejercicio física, Vitamina D, Interleucina-10, Niños; Adolescentes.

1. Introduction

Us Studies with children and adolescents that address health indicators of this population, published in the last decade, have described the benefits of physical activity, and the levels of vitamin D, which in turn is an essential hormone in the regulation of calcium and phosphorus metabolism and that it plays a key role in an individual's bone health. Emerging evidence in recent years suggests that vitamin D also exerts a variety of extra-skeletal physiological actions, although its clinical consequences are still debated(Blakeley et al., 2018; Valtueña Santamaría et al., 2013) and as an immunomodulatory response to production of IL-10 (anti-inflammatory cytokine) has its contribution in the health of children and adolescents by mediating protective factors of vascular endothelium, endocrine tissue, perivascular tissue differentiation (PVAT), also adjuvant for the regulation of blood glucose levels and as a stimulant endocrine to the parathyroid (Alghadir et al., 2018; Jiménez-Pavón et al., 2014).

Studies have recently begun to compare the health impacts of specific combinations of these physical activity, vitamin D and interleukin-10 but this evidence has yet to be reviewed or synthesized.

Studies that assessed vitamin D status in childhood and adolescence and together demonstrated widespread hypovitaminosis D worldwide, from childhood to young adulthood, physical fitness is considered to contribute to vitamin D indices (Jiménez-Pavón et al., 2014; Narchi et al., 2015).

Thus, the purpose of this protocol was to describe the aims and methods for a systematic review to summarize the studies examining the influence of physical activity and vitamin D on serum levels of interleukin -10 in children and adolescents.

2. Methodology

The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42020187368 (http://www.crd.york.ac.uk/PROSPERO). The Preferred Reporting Items of Systematics Reviews and Meta-Analyses (PRISMA-P)(Moher et al., 2016) will guide the report of this systematic review and this protocol was prepared and written according to PRISMA-Protocol.

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

Table 1.

Section and topic	Item No	Checklist item	Page
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	NA
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	2
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	2
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	2
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			5
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	5-6
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	8-9
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	Suplementary file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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)	10
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	9-10
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	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9

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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

* 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.

The systematic review will include studies that meet the following eligibility criteria based on the Population, Intervention, Control, Outcome and Study design framework (PICOS framework) (Stylianou et al., 2020).

Studies will be accepted when the sample is composed by individuals aged 09 to 13y.

For experimental studies, interventions will have to target at least two of the three movement behaviors (both physical activity and sedentary behavior). For observational studies, exposure will be any combination of two or three movement behaviors (ie, sleep, sedentary lifestyle, and physical activity). Briefly, interventions / exposures relevant to each individual movement behavior will be operationalized as durations (sleep, sedentary lifestyle and physical activity), patterns and types (sedentary lifestyle and physical activity) and intensities (physical activity) of the behaviors. The rationale for these decisions was based on previous systematic reviews of the relationship between movement behaviors and health outcomes in children and adolescents (Aguiar et al., 2016a, 2016b; Calvo & Lamberg-Allardt, 2017; Fuleihan et al., 2006; Hoy et al., 2012; MGregory et al., 2013; Moreno et al., 2011). No limits on the measurement method (ie self-reported, accelerometer-based) for any of the behaviors will be imposed.

The comparator will be various durations and combinations of movement behaviors. However, a comparator group or control group will not be required for inclusion.

Critical health indicators will be adiposity (ie, body mass index [BMI], skinfolds, body fat, waist circumference), fitness (eg, cardiovascular fitness, musculoskeletal fitness), bone, and skeletal health (eg, bone mineral content, bone mineral density), cardiometabolic health (eg, blood pressure, glucose, insulin resistance, blood lipids) (Carson et al., 2015; Ouzzani et al., 2016; Saggese et al., 2018; Saunders et al., 2016; Shamseer et al., 2015).

To be included, studies must report the measure of effect and/or association for the relationship between any combination of physical activity, serum vitamin D, and interleukin-10 in adolescent children and at least one of these health outcomes, which may be linear (ie, regression coefficients, mean differences, effect sizes) or categorical statistical parameters (ie, odds ratio, hazard ratio).

All observational studies that examine the association of combinations of physical activity, serum vitamin D, and IL-10 levels with at least one of the health outcomes will be included, as well as experimental studies that employ interventions that focus on combining at least two behaviors. (Sedentary lifestyle and physical activity).

An electronic search of the literature will be carried out in six databases and two repositories of studies:

1) Medline (PubMed)

2) Embase(Sciense Direct)

3) Bireme/Lilacs (BVS)

4) Scopus

5) EBSCO

6) Cochrane clinical trials

Keywords will be selected by assessment of the Medical Subject Headings (MeSH) in the National Library of Medicine and relevant text to the area. The organization of search terms will be carried out according to the PICOS framework[9].The search strategy for each of the following databases is presented in Table 2.

Table 2. Search strategy (PROSPERO register: CRCRD42020187368).

Draft search strategy for each electronic databases queried: Medline (PubMed), Scopus, Web of Science, Sciense Direct, Embase and Cochrane clinical trials. For each search listed below, no start date and language were applied, and databases were searched from their inception or date of the earliest available publication.

Data base	Pubmed (including Medline)	Number os articles reached
1#	"Child"[Mesh] OR (Children)	
2#	"Adolescent"[Mesh] 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)	
3#	"Exercise"[Mesh] 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 (Acute Exercise) OR (Acute Exercises) OR (Exercise, Acute) OR (Exercises, Acute) OR (Exercise, Isometric) OR (Exercises, Isometric) OR (Isometric Exercises) OR (Isometric Exercise) OR (Exercise, Aerobic) OR (Aerobic Exercise) OR (Aerobic Exercises) OR (Exercises, Aerobic) OR (Exercise Training) OR (Exercise Trainings) OR (Training, Exercise) OR (Trainings, Exercise)	
4#	"Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR (Calciol) OR ((3 beta,5Z,7E)- 9,10-Secocholesta-5,7,10(19)-trien-3-ol) OR (Vitamin D 3) OR (Vitamin D3) OR (Cholecalciferols)	
5#	"Interleukin-10"[Mesh] OR (Interleukin 10) OR (IL10) OR (IL-10) OR (CSIF-10) OR (Cytokine Synthesis Inhibitory Factor)	
5#	(1# AND 2#) OR (1# AND 3#) OR (2# AND 3#)	
6#	#4 AND #6	

Data base	**EMBASE**	Number os articles reached
1#	'child'/exp OR (children)	
2#	'adolescent'/exp OR (teenager)	
3#	'physical activity'/exp OR (activity, physical)	
4#	'colecalciferol'/exp OR (9, 10 secocholesta 5, 7, 10 (19) trien 3 ol) OR (activated 7 dehydrocholesterol) OR (arachitol) OR (baby d) OR (bonesyl) OR (calciol) OR (cholecalciferol) OR (cholecalciferols) OR (d mulsin) OR (d tracetten) OR (d3 vicotrat) OR (ddrops) OR (desunin) OR (devaron) OR (duphafral) OR (dupharinterfran) irradia) OR (irradian) OR (kora liquid) OR (liquid (vitamin D3)) OR (ostoforte) OR (uvedose) OR (vi-de 3) OR (vigantol) OR (vigorsan) OR (vitamin d 3) OR (vitamin D3)	
5#	'interleukin 10'/exp OR (csif) OR (cytokine synthesis inhibitory factor) OR (il 10) OR (il-10) OR (interleukin-10)	
6#	(1# AND 3#) OR (2# AND 3#) OR (1# AND #2 AND #3 AND 4#)	

Data base	Bireme/LILACS (BVS)	Number os articles reached
1#	MH: "Criança" OR (Niño) OR (Child) OR (Crianças) OR MH:M01.060.406$	
2#	MH: "Adolescente" OR (Adolescente) OR (Adolescent) OR (Adolescentes) OR (Jovem) OR (Jovens) OR (Adolescência) OR (Juventude) OR MH: M01.060.057$	
3#	MH: "Atividade Física" OR (Atividade Locomotora) OR (Atividade Motora) OR (Actividad Motora) OR (Motor Activity) OR MH: F01.145.632$ OR MH: G11.427.590.530.698$	
4#	MH: "Vitamina D" OR (Vitamina D) OR (Vitamin D) OR MH:D04.808.812.768$	
5#	MH: "Interleucina-10" OR (Interleucina-10) OR (IL-10) OR MH:D12.644.276.374.465.510$ OR MH: D12.776.467.374.465.510$ OR MH: D23.529.374.465.510$	
6#	1# AND 2# AND 3# AND 4# AND 6#	

Data base	**Cochrane**	Number os articles reached

1#	(Child) OR (Children)
2#	(Adolescent) OR (Male Adolescent) OR (Adolescents, Male) OR (Male Adolescents) OR (Adolescent, Male) OR (Youths) OR (Youth) OR (Adolescence) OR (Teenagers) OR (Teens) OR (Teen) OR (Teenager) OR (Adolescents) OR (Adolescents, Female) OR (Adolescent, Female) OR (Female Adolescent) OR (Female Adolescents)
3#	(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 (Acute Exercise) OR (Acute Exercises) OR (Exercise, Acute) OR (Exercises, Acute) OR (Exercise, Isometric) OR (Exercises, Isometric) OR (Isometric Exercises) OR (Isometric Exercise) OR (Exercise, Aerobic) OR (Aerobic Exercise) OR (Aerobic Exercises) OR (Exercises, Aerobic) OR (Exercise Training) OR (Exercise Trainings) OR (Training, Exercise) OR (Trainings, Exercise)
4#	(Vitamin D) OR (Cholecalciferol) OR (Calciol) OR ((3 beta,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol) OR (Vitamin D 3) OR (Vitamin D3) OR (Cholecalciferols)
5#	(Interleukin-10 Receptor, beta Chain) OR (Interleukin-10 Receptor 2) OR (Interleukin 10 Receptor, beta Chain) OR (Interleukin 10 Receptor beta Subunit) OR (Interleukin 10 Receptor 2)
6#	(1# AND 2# AND 3# AND #4 AND #5)

Data base	**Scopus** Number os articles reached
1#	TITLE-ABS-KEY (Child) OR (Children)
2#	TITLE-ABS-KEY (Adolescent) OR (Male Adolescent) OR (Adolescents, Male) OR (Male Adolescents) OR (Adolescent, Male) (Youths) OR (Youth) OR (Adolescence) OR (Teenagers) OR (Teens)
3#	TITLE-ABS-KEY (Exercise) OR (Exercises) OR (Physical Activity) OR (Activities, Physical) OR (Activity, Physical) OR (Physical Activities) OR (Exercise, Physical) OR (Exercises, Physical) OR (Physical Exercise)
4#	TITLE-ABS-KEY (Vitamin D) OR (Cholecalciferol) OR (Calciol)
5#	TITLE-ABS-KEY (Interleukin-10 Receptor, beta Chain) OR (Interleukin-10 Receptor 2) OR (Interleukin 10 Receptor, beta Chain)

Source: Authors.

We will use additional search strategy to further explore the grey literature, as following:

Consultation of the reference lists of all original articles included: we will review references of each included study and review studies in the field to identify potential studies not found in the initial search:

Contact with the authors: (i) if complete articles are not available; and (ii) if certain data are not available in the original article, such as data presented only in graphs.

Searches in repositories of clinical trials: The ClinicalTrials.gov (http://clinicaltrials.gov/) will be also consulted and eligibility criteria will be applied to the original studies and those in the repositories for inclusion in this review. If we find eligible studies that are unpublished, we will contact the authors to obtain the results.

A software (Rayyan) (Ouzzani et al., 2016) will be used for management of references and duplicates removal. Subsequently, the data will be continued in the Rayyan software, so the screening process can be performed. The review process is presented below in a step-by-step fashion.

Following the search in databases, all references will be transferred to a single Rayyan for subsequent duplicate removal, using the "find duplicates" tool. A manual check of all references will be performed to ensure that all duplicates have been removed. Subsequently, all references will be transferred to the Rayyan QCRI software[23] with the intention to enable independent selection by two experienced reviewers.

To reduce disagreements in the selection process between the two reviewers, a pilot screening will be performed by selecting 20 articles randomly. For that, each article will be jointly reviewed by the reviewers to improve decision making.

Afterwards, the selection process will be started with all references, which will be carried out in two levels: (i) the reviewers will read all titles and abstracts of the articles; (ii) the reviewers will read all articles in full.

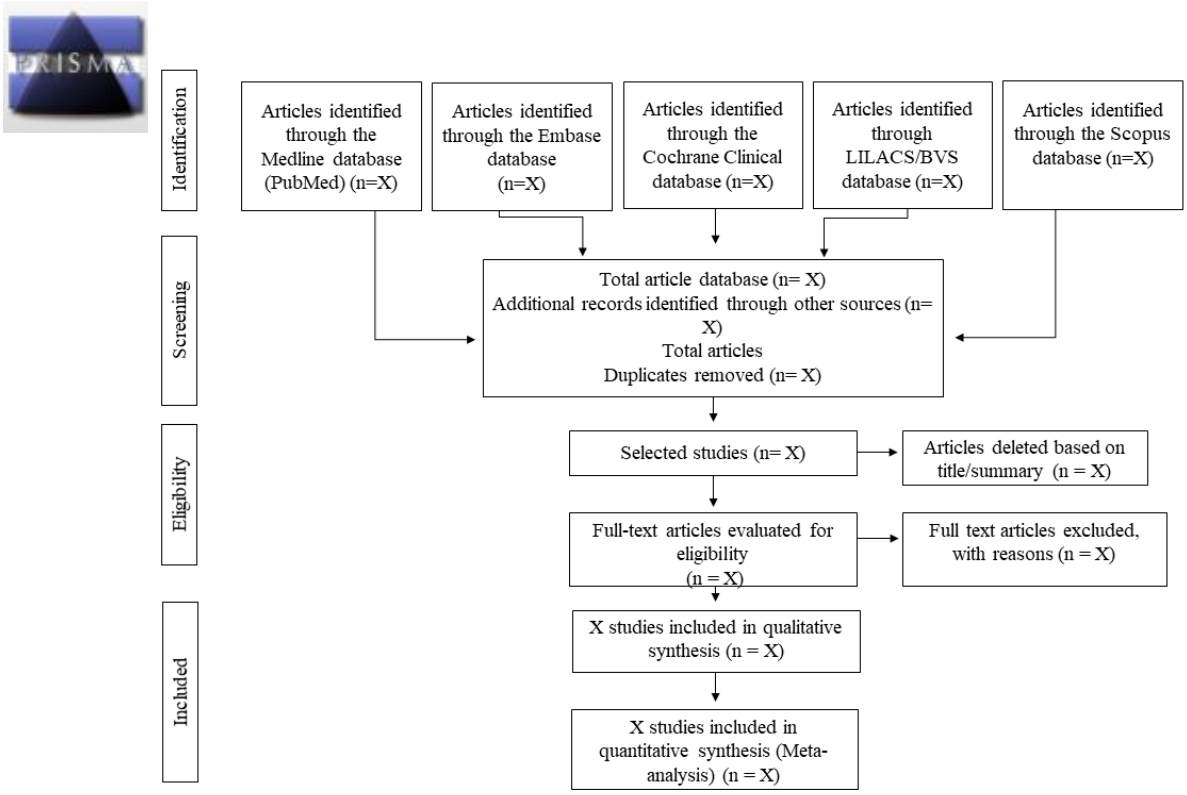
In the first level, a screening based on the reading of the title/abstract of the articles will be performed according to the eligibility criteria. After that, a consensus meeting will be performed to evaluate the selection of articles to be screened at the second level (full text reading) and any divergences will be resolved by consulting a third reviewer. Following this

meeting, the full text of the articles will be downloaded and stored in two folders (one for each reviewer) and two spreadsheets with identical contents will be for full post-read selection.

In the second level, the reviewers will read the full texts. At this stage, the reviewers will evaluate the defined eligibility criteria. Exclusions will be justified within the Rayyan software and a third reviewer will be used to resolve disagreements. After this selection, another consensus meeting will be held to review which articles will be considered eligible for review. If necessary, a third reviewer will also be used to resolve disagreements. After the selection process in electronic databases, complementary search strategies (author contact and reference list screening) will be employed by one reviewer to identify additional studies. The research development process flow diagram is presented in Figure 1, according to the PRISMA guidelines (*Cochrane Handbook for Systematic Reviews of Interventions* | *Cochrane Training*, n.d.).

Figure 1. Prisma Flow.

PRISMA 2009 Flow Diagram



From: Moher D, Liberti A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

All stages of data extraction, management, risk of bias, level of evidence rating, and synthesis will be independently implemented by two reviewers. In the case of disagreement, a third reviewer will be consulted.

Reviewers will receive a spreadsheet (elaborated by the authors) in Excel format with all the variables to be filled by them (Template for data extraction). Briefly, the extracted data will include the study descriptive information (year of publication, study design, country in which the study was conducted, number of participants, sex, age range), relevant intervention/exposure (method used to assess time spent in the physical activity and method for operationalizing the combination of the behaviours), health outcome details, statistical procedures, as well as study results. When studies presented unadjusted and adjusted results, extraction data will include the results from the unadjusted model and the most fully adjusted one in Table 3.

Table 3. Template for data extraction.

T	Variables reference	Content Author, year, study	 designe	Il-10	Outcomes (sun exposure, Insulin resistance, BMI, Lipid profile)
Study profile	Study type Country study				
Population	Range-age-sample				
Exposure	Physical activity Vitamin D				
Outcome	Il-10, BMI, sun exposure, Insulin resistance, lipid profile				

Source: Authors.

The study quality tool of the Joanna Brigs (JBI) (https://synthesismanual.jbi.global)(Moola et al., 2020) which provide appropriate tools for each study design (ie. intervention studies, cohort, and cross-sectional studies), will be employed (**Risk of bias (methodological quality) assessment**) Figure 2.

Figure 2. (Risk of bias (methodological quality) assessment).

Quality Assesment Tool for Cross-Seccional Studies	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
2. Were the study subjects and the setting described in detail?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were objective, standard criteria used for measurement of the condition?	□	□	□	□
5. Were confounding factors identified?	□	□	□	□
6. Were strategies to deal with confounding factors stated?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was appropriate statistical analysis used?	□	□	□	□

Quality Assesment Tool for Randomised Controlled Trials

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	□	□	□	□
2. Was allocation to treatment groups concealed?	□	□	□	□
3. Were treatment groups similar at the baseline?	□	□	□	□
4. Were participants blind to treatment assignment?	□	□	□	□
5. Were those delivering treatment blind to treatment assignment?	□	□	□	□
6. Were outcomes assessors blind to treatment assignment?	□	□	□	□
7. Were treatment groups treated identically other than the intervention of interest?	□	□	□	□
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	□	□	□	□
9. Were participants analyzed in the groups to which they were randomized?	□	□	□	□
10. Were outcomes measured in the same way for treatment groups?	□	□	□	□
11. Were outcomes measured in a reliable way?	□	□	□	□
12. Was appropriate statistical analysis used?	□	□	□	□
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	□	□	□	□

Source: Authors.

The tool includes 14 items for assessing potential flaws in study methods or implementation, including sources of bias (ie. participants' selection, performance, attrition, and detection), confounding, study power, the strength of causality in the association between interventions/ exposures and outcomes, and other factors. The possible answers to the 14 questions are "yes", "no", or "cannot determine/not reported/not applicable". Whenever the answer "no", "CD, or "NR" is selected, it will be considered that a potential risk of bias could be introduced by that flaw in the study design or implementation.

Two independent reviewers will critically assess the risk of bias in studies referred in the synthesis. A consensus meeting will take part and, when necessary, a third reviewer will be consulted for resolution of doubts, agreement, or consensus. No study will be excluded based on assessment of the risk of bias; on the contrary, the methodological rigor of each study will be considered for the confidence assessments of each finding in the review. Nevertheless, the strengths and methodological limitations of the studies will be discussed among the authors until a consensus is reached. This will be done based on each item and its impact on the main inferences from the studies and the review. In other words, the use of the total scores or the classification of the methodological quality of the included studies will not be applied.

The meta-analyses will be performed in software Review Manager V.5.4 (*RevMan* | *Cochrane Training*, 2019)(revman.cochrane.org). We will synthesize the data using random effects meta-analysis for results that are sufficiently homogeneous in terms of statistical, clinical, and methodological characteristics (revman.cochrane.org). If not, then a narrative synthesis for each outcome will be conduct ed. If the data allow it, our narrative syntheses or meta-analyses will be conducted, with all studies weighted equally and structured by health outcome, study design, and combination of physical activity, vitamin D serum and IL-10 levels. Anticipating a high heterogeneity in study designs, protocols of measurement and combination of the physical activity.

In the presentation of data, the results will be first organized in alphabetical order by the main authors; if the first author is repeated, we will organize the articles in chronological order by the year of publication. All forest plots will also be grouped by the type of study. In the case of modification of the protocol in the completed publication of the results of this systematic review, the authors will clarify and justify all modifications in a specific section. Risk of Bias estimate with Cochrane(Higgins et al., 2011) will be used to assess quality of evidence across studies. Quality of evidence will be rated as "very low", "low", "moderate", or "high" based on five criteria: risk of bias, inconsistency, indirectness, imprecision, and other (ie. dose-response evidence). Except for randomized controlled trials that will start at "high" rating, all studies will start will "low" quality. Subsequently, quality of evidence will be downgraded regardless of study design if studies have limitations in any of the five criteria. If no downgrading occurred, non-randomized and observational study designs presenting large or very large effect sizes and/ or dose-responses could be upgraded to "moderate" or "high" quality of evidence. However, as dose-response evidence cannot be determined for cross-sectional studies, so the quality of evidence in these studies will be upgraded only if there is a gradient of higher exposure with higher/lower health indicator.

3. Results and Discussion

Data synthesis and statistical analysis of the influence of physical activity, vitamin D and serum levels of Interleukin-10 in children and adolescents, will be carried out by the authors. If possible, Meta-analysis will be carried out using REVMAN 5.3. Heterogeneity between studies included will be examined using the I2 statistic and p-value. We will consider evidence of significant heterogeneity when a P-value is less than 0.10 or when we find a large I2 statistic (I2 75 %). In such a case, we will perform sensitivity analysis as required. A random-effect model will be used since we may have data from widely differing population sources. Risk ratio will be changed to analyze when binary data existence.

Data summarization will involve a quantitative component, which synthesizes the frequency using simple percentage and the main characteristics of the studies, and a qualitative component, to outline the underlying concepts/theories and the elements and structures of the conceptual models identified in the search.

Quantitative data will be displayed in the form of charts, tables and graphic elements. The qualitative analysis will be guided by the expositions and key points identified by the authors classified into categories defined from the reading of the articles, and then a narrative synthesis will be produced. In addition, a summary chart of each study will be made available as supplementary material to the systematic review study.

Evidence directly relates the practice of physical activities with anti-inflammatory markers such as IL-10 and adiponectin, sun exposure to vitamin D insufficiency levels in children and adolescents, plus the practice of physical activity (Gleeson et al., 2011; Healy et al., 2011; Sam et al., 2009; Yates et al., 2012). Vitamin D interacts with cells of innate and adaptive immunity, and T reg cells are activated when there is hypovitaminosis D (Bikle, 2014; Vimaleswaran et al., 2013).

Interleukin 10 plays an anti-inflammatory function and is inversely correlated with body fat mass, being an indicative marker as well as subclinical systemic inflammation. Studies describe that sedentary behavior induced lower levels of anti-inflammatory interleukin essentially IL-10 (Healy et al., 2011; Sam et al., 2009; Tauler et al., 2016; Yates et al., 2012).

No Systematic Review has been performed describing the influence of physical activity, vitamin D and serum levels of Interleukin-10 in children and adolescents to date. This protocol has some limitations, such as different inflammatory markers, age group of the population, measures to assess results, which can generate some bias.

We intend to publish this review in a peer-reviewed journal, and this will be included as a result of a doctoral thesis. It is expected that the information generated with the systematic review will collaborate with the continuity of studies with physical activity, vitamin D to verify its influence action and degree of evidence.

The final review report will follow the recommended in the checklist according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Scoping Reviews (PRISMA-ScR) extension (Tricco et al., 2018).

4. Conclusion

The practice of physical activity continues to be relegated to the world population, even when it comes to children and adolescents, a transitional and vulnerable phase to the implementation of healthy habits.

This protocol may provide evidence on the influence of physical activity, vitamin D and serum levels of Interleukin-10 in children and adolescents, which will contribute to possible behaviors of healthy behavior aimed at this age group, considering collective health worldwide.

It is hoped that one of the findings compiled from this review will support the development of notes and guidelines for the field of health education.

In addition, future research that seeks to identify issues related to the influence of physical activity, vitamin D and serum levels of Interleukin-10 in children and adolescents, to face a sedentary lifestyle and uncertainties still present about vitamin D and its immunomodulatory potential.

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