Core outcomes in children and adolescents with overweight/obesity exposed to physical activity interventions: protocol for the development of a core outcome set

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ABSTRACT

Introduction: High-quality experimental studies to assess pragmatic and effective interventions to increase levels of physical activity and/or improve health status in children and adolescents are still needed, especially on those with overweight and obesity. Furthermore, inconsistency and outcome-reporting bias across studies, what can preclude important comparisons between them, could be reduced with the development of core outcome sets (COS) (i.e., a list of minimum outcomes that should be measured and reported in all trials for a specific clinical area). Therefore, our aim is to develop a COS related to clinical trials with physical activity interventions for overweight or obese children and adolescents, as well as categorize them into specific domains.

Methods and analysis: A list of outcomes will be generated in three steps for later use in an online Delphi survey : (1) an overview of systematic reviews with or without meta-analyses; (2) qualitative interviews with stakeholder groups; (3) review of the final outcome list by study members. The stakeholders involved in the COS consensus process will be trialists, clinicians, physical education teachers, parents/caregivers of children and adolescents. The Delphi exercise will involve two to three rounds in order to achieve consensus. The scoring system will involve a 9-point Likert scale where outcomes are graded in accordance with their level of importance. All outcomes from the list presented in round 1 will be retained in round 2. Items will be retained from the end of round 2 to the CORE set using stricter cut-off criteria; retained items will be those rated between 7 and 9 by over 70% of respondents and 1 to 3 by less than 15% in at least one stakeholder group.

Ethics and dissemination: The present study will be submitted to the research ethics committee. We aim to disseminate the COS methods and findings to as many stakeholders as possible. The dissemination plan after COS completion encompasses the following: (1) scientific manuscripts; (2) dissemination in digital media; (3) communication via email with stakeholders involved.

COMET registration: #1356 / <http://www.comet-initiative.org/Studies/Details/1356>

INTRODUCTION

Overweight and obesity in childhood is a health condition that globally affects wealthy as well as low- and middle-income countries (LMICs), particularly in urban settings. The WHO predicts 158 million obese children aged 5-19 years at 2020 [1]. In this last estimate, an additional 216 million children were considered overweight [2]. Overweight and obesity in childhood and adolescence are associated with greater risk and earlier onset of cardiometabolic morbidity [3,4]. Furthermore, these conditions bear other consequences such as adverse psychosocial effects and lower educational attainment [5–7].

Obesity is a multifactorial disease which comprises a combination of biological, genetic, social, environmental, and behavioral determinants [8,9]. The association between physical inactivity and overweight/obesity is established in the literature [8,9] and a vicious circle may arise between decreasing physical activity and weight gain from childhood to early adulthood [10]. Therefore, sedentary behavior in children and adolescents is a growing public health problem that ultimately relates to the prevalence of overweight and obesity at varied life stages. Current guidelines from the World Health Organization (WHO) recommend that children and adolescents engage in at least 60 min of physical activity of moderate to vigorous intensity on all or most days of the week [11,12]. However, about 80% of adolescents were not meeting such guidelines recommendations worldwide [11–13]. Among Brazilian children and adolescents the prevalence of physically active, based on the WHO guidelines, is lower than 50% [14].

Several existing interventions targeting reduction in sedentary time of children and adolescents showed efficacy but not effectiveness [15]. Therefore, high-quality experimental studies to assess pragmatic interventions (i.e. less structured, multiple modality, and longer term) that may provide effectiveness to increase levels of physical activity and/or improve health status in children and adolescents are still needed. Primary studies have investigated interventions that are mostly based on either 1) counselling to reduce sedentary behavior and increase physical activity or 2) structured physical activity programs, inside or outside the school environment, involving parents or not.

Although some heterogeneity at the level of interventions is even desirable, allowing to contrast comparable methodological differences and subsequently provide models for pragmatic and cost-effective implementation, it is important to establish consistent and

comparable outcomes across studies. Indeed, difficulties caused by heterogeneity in outcome measurement are a common issue to systematic reviewers aiming to summarize and provide inferences about the existing evidence in different research fields. These issues of inconsistency and outcome-reporting bias could be reduced with the development and application of agreed standardized sets of outcomes, known as core outcome sets (COS), that should be measured and reported in all trials for a specific clinical area [16]. In addition, even though the number of COS projects has been increasing, the involvement of stakeholders from LMICs in the development of COS is still low [17]. Because overweight and obesity are conditions influenced by social and environmental features [18,19], the input from key stakeholders from varied settings may enrich the discussion and choice of outcomes that will compose a COS in a more representative way.

Accordingly, we aim to report the protocol for development of a COS related to clinical trials with physical activity interventions for overweight or obese children and adolescents, as well as categorize them into specific domains. To identify existing knowledge, a search of the Core Outcome Measures in Effectiveness Trials (COMET) initiative database (<http://www.comet-initiative.org/>) was completed prior to this project.

METHODS

This protocol was outlined according to the Core Outcome Set-STAndards for Development (COS-STAD) [20] and reported according to the Core Outcome Set-STANDARDISED Protocol Items (COS-STAP) [21]. The COS development study was registered in the COMET Initiative (<http://www.comet-initiative.org/studies/details/1356>).

Scope

The application of COS will be in clinical research investigating lifestyle interventions with a physical activity component to improve health outcomes in children and adolescents with overweight or obesity. The specifications of population and interventions are:

- 1) Children and adolescents (from 5 to 18 years old) presenting overweight or obesity with or without cardiometabolic comorbidities (i.e., hypertension and diabetes).
- 2) Physical activity interventions alone or in combination with other interventions (e.g., diet intervention or behavioral intervention) will be considered. To cover interventions of physical activity comprehensively, we will take into consideration

structured exercise programs, educational materials on physical activity, face-to-face counseling (without individually tailored prescriptions). In addition, we will consider interventions that are implemented to parents or caregivers as mediators to promote physical activity and modify outcomes in children and adolescents.

Stakeholders

The stakeholder groups to be involved in the COS consensus process are:

- 1) Trialists: This group will comprise authors from publications with physical activity interventions to children and adolescents with overweight/obesity, identified in the overview of quantitative literature. We will initially contact corresponding authors of all trials included in systematic reviews summarized in our overview study (PROSPERO, CRD42019120334).
- 2) Clinicians: This group will comprise health professionals (e.g., physicians, nurses, nutritionists) from the divisions of endocrinology and pediatrics at the Hospital de Clínicas de Porto Alegre. We will invite only those individuals who are involved in regular healthcare of children and adolescents with overweight/obesity.
- 3) Physical education teachers: This group will comprise physical education teachers of public and private schools in Porto Alegre, Brazil. We plan to compose this group with five to six individuals to allow representativeness of teachers working in heterogeneous grades and poor/rich neighborhoods.
- 4) Parents/Caregivers of children: This group will comprise parents or primary caregivers of children with overweight/obesity. We plan to reach this group through facilitation of parent-teacher-student associations in public and private schools in Porto Alegre.
- 5) Adolescents: This group will comprise adolescents with overweight/obesity from public and private schools in Porto Alegre, Brazil who volunteer to participate in initial interviews and subsequent Delphi rounds.

Information sources

The list of outcomes for use in an online Delphi survey will be generated in three steps from the following sources:

Step 1: An overview of systematic reviews with or without meta-analyses (PROSPERO, CRD42019120334) will be used as sources of clinical trials. Therefore, eligible studies for this

overview are as follows: 1) consisting of systematic reviews with or without meta-analyses of interventional studies (randomized or non-randomized, controlled or non-controlled), written in English, Portuguese or Spanish; 2) including populations of children and/or adolescents (from 5 to 18 years old) healthy or without illness diagnoses other than those related to cardiometabolic conditions associated with lifestyle and behavior; 3) intervening, for at least 4 weeks, with programs of physical activity (e.g., exercise program) directly for children and/or adolescents or indirectly through educational materials (e.g., leaflets, mobile applications) or programs toward parents/caregivers; 4) reporting of health outcome measured in children or adolescents. Data selection and extraction will be carried out independently by peer. The following information was extracted from studies: outcomes and their assessment measures, number of clinical trials included, number of participants and their characteristics (e.g. age, sex and health status), type of interventions and setting. After extraction, outcomes will be grouped into specific domains according to similarity.

Step 2: Qualitative interviews to complement the results from the literature review and allow a deeper understanding of which outcomes are valued by each stakeholder group. Because we anticipate that Step 1 will provide us with the outcomes most relevant to trialists, such interviews will be conducted face-to-face with clinicians, physical education teachers, parents/caregivers, and adolescents. The interviews will be semi-structured, recorded and transcribed.

Step 3: Review of the final outcomes list. The outcomes list will then be reviewed by study members to ensure that the outcome description is clear, that have been grouped appropriately into the specific domains, and that there are no duplications within the outcomes. Outcomes with similar definitions or themes will be merged. The initial list comprises the outcomes in a randomized order.

Consensus process

The Delphi exercise will involve two to three rounds in order to achieve consensus among a panel of international stakeholders.

Selection of stakeholders

Stakeholder groups will be invited by email to participate in the consensus process. The number of participants invited will be documented, as well as the number of those who accepted and completed rounds 1 and 2 (attrition assessment). To minimize attrition bias, we will only invite people who respond to the preliminary invitation to participate in the first Delphi round [22]. In addition, we will send periodic reminders to emphasize to participants the importance of completing the whole Delphi exercise.

Scoring system

The scoring system will involve a 9-point Likert scale where outcomes are graded in accordance to their level of importance regarding to or based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [23]: 1 to 3 signifies that an outcome is of limited importance, 4 to 6 is important but not critical, and 7 to 9 critical [16]. An option of “unable to score” will also be included to allow for the fact that some stakeholder group members may not have the level of expertise to score certain outcomes.

Round 1

The list that will be developed in step 3 will be presented at the Delphi round 1. In the first round, a link to the electronic version of the Delphi questionnaire, including instructions for completion, will be sent by email to the participants. The outcomes will be grouped into domains.

After participating in round 1, the stakeholders will receive feedback. The results for each outcome will be aggregated across participants and descriptive statistics will be presented [16].

Round 2

In round 2, participants will be asked to review the score provided in round 1 for each one of the retained outcomes. Feedback will be provided for participants from their score of round 1 and from all stakeholder groups separately, which is likely to facilitate consensus between groups [24]. The participants will be asked to consider responses from the other members and asked to rescore the outcomes.

Consensus definition

All outcomes from the list presented in round 1 will be retained in round 2, enabling participants to score the list of outcomes as a whole [16]. Items will be retained from the end of round 2 to the CORE set using stricter cut-off criteria; retained items will be those rated between 7 and 9 by over 70% of respondents and 1 to 3 by less than 15% in at least one stakeholder group [16].

ETHICS and DISSEMINATION

The present study will be submitted to the research ethics committee of Hospital de Clínicas de Porto Alegre. We aim to disseminate the COS methods and findings to as many stakeholders as possible. The dissemination plan after COS completion encompasses the following: (1) scientific manuscripts; (2) dissemination in digital media; (3) communication via email with stakeholders involved. The manuscripts will be reported according to COR-STAR statement [25].

ADMINISTRATIVE INFORMATION

Funders

The study will be supported by Fundo de Incentivo à Pesquisa e Eventos of Hospital de Clínicas de Porto Alegre (FIPE-HCPA, Brazil) and by National Institute of Science and Technology for Health Technology Assessment (IATS, Brazil).

Conflicts of interest

All the authors do not have any personal, financial or cultural potential conflict of interest related to this work to declare.

References

1. World Obesity Federation. Atlas of Childhood Obesity. Edited by Tim Lobstein and Hannah Brinsden World Obesity Federation. 2019;
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. 2017;390:2627–42.
3. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes*. 2011;35:891–8.
4. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-Term Morbidity and Mortality of Overweight Adolescents [Internet]. *New England Journal of Medicine*. 1992. p. 1350–5. Available from: <http://dx.doi.org/10.1056/nejm199211053271904>
5. Quek Y-H, Tam WWS, Zhang MWB, Ho RCM. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. *Obes Rev*. 2017;18:742–54.
6. Caird J, Kavanagh J, O'Mara-Eves A, Oliver K, Oliver S, Stansfield C, et al. Does being overweight impede academic attainment? A systematic review [Internet]. *Health Education Journal*. 2014. p. 497–521. Available from: <http://dx.doi.org/10.1177/0017896913489289>
7. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics*. 2012;130:e856–64.
8. Gray CL, Messer LC, Rappazzo KM, Jagai JS, Grabich SC, Lobdell DT. The association between physical inactivity and obesity is modified by five domains of environmental quality in U.S. adults: A cross-sectional study. *PLoS One*. 2018;13:e0203301.
9. Fox KR, Hillsdon M. Physical activity and obesity. *Obes Rev*. 2007;8 Suppl 1:115–21.
10. Pietiläinen KH, Kaprio J, Borg P, Plasqui G, Yki-Järvinen H, Kujala UM, et al. Physical inactivity and obesity: a vicious circle. *Obesity*. 2008;16:409–14.
11. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. *Int J Behav Nutr Phys Act*. 2011;8:98.
12. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2015.
13. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects [Internet]. *The Lancet*. 2012. p. 247–57. Available from: [http://dx.doi.org/10.1016/s0140-6736\(12\)60646-1](http://dx.doi.org/10.1016/s0140-6736(12)60646-1)

14. Filho VCB, da Costa RM, Knebel MTG, de Oliveira BN, de Araújo Silva CB, da Silva KS. The prevalence of global physical activity among young people: a systematic review for the Report Card Brazil 2018 [Internet]. *Brazilian Journal of Kinanthropometry and Human Performance*. 2018. p. 367–87. Available from: <http://dx.doi.org/10.5007/1980-0037.2018v20n4p367>
15. Altenburg TM, Holthe JK, Chinapaw MJM. Effectiveness of intervention strategies exclusively targeting reductions in children’s sedentary time: a systematic review of the literature [Internet]. *International Journal of Behavioral Nutrition and Physical Activity*. 2016. Available from: <http://dx.doi.org/10.1186/s12966-016-0387-5>
16. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. *Trials*. 2017;18:280.
17. Davis K, Gorst SL, Harman N, Smith V, Gargon E, Altman DG, et al. Choosing important health outcomes for comparative effectiveness research: An updated systematic review and involvement of low and middle income countries. *PLoS One*. 2018;13:e0190695.
18. Rocha SGM, Sabrina G M, Rocha HAL, Leite ÁJM, Machado MMT, Lindsay AC, et al. Environmental, Socioeconomic, Maternal, and Breastfeeding Factors Associated with Childhood Overweight and Obesity in Ceará, Brazil: A Population-Based Study [Internet]. *International Journal of Environmental Research and Public Health*. 2020. p. 1557. Available from: <http://dx.doi.org/10.3390/ijerph17051557>
19. Campbell MK. Biological, environmental, and social influences on childhood obesity. *Pediatr Res*. 2016;79:205–11.
20. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. *PLoS Med*. 2017;14:e1002447.
21. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndardised Protocol Items: the COS-STAP Statement. *Trials*. 2019;20:116.
22. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Med*. 2011;8:e1000393.
23. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64:395–400.
24. Brookes ST, Macefield RC, Williamson PR, McNair AG, Potter S, Blencowe NS, et al. Three nested randomized controlled trials of peer-only or multiple stakeholder group feedback within Delphi surveys during core outcome and information set development. *Trials*. 2016;17:409.
25. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement [Internet]. *PLOS Medicine*. 2016. p. e1002148. Available from: <http://dx.doi.org/10.1371/journal.pmed.1002148>