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Evaluation of the effect of physical exercise interventions in Primary Health Care in Brazil on cardiometabolic risk factors: a systematic review

Avaliação do efeito de intervenções de exercícios físicos na Atenção Primária à Saúde no Brasil sobre fatores de risco cardiometabólicos: uma revisão sistemática

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Abstract – The objective was to systematically search and synthesize the evidence available in the literature about the effect of physical exercise interventions Primary Health Care (PHC), carried out in Brazil, on cardiometabolic risk factors. The search was performed in the PubMed, Virtual Health Library and Web of Science databases. The inclusion criteria were: studies with physical activity (PA) interventions or exercise in PHC; carried out in Brazil; population aged >18 years; at least one cardiometabolic risk factor assessed pre and post-intervention. The "Health Sciences Descriptors" were used to define the search descriptors: "physical activity" OR "exercise" OR "motor activity" AND "primary health care" OR "health centers" OR "primary care" AND "Brazil". The selection phases were performed by pairs of blinded researchers and the conflicts were decided by a third evaluator. Jadad scale was used to assess the methodological quality of the articles included. In total, 1,817 articles were found and 26 duplicates excluded, leaving 1,791 for reading of titles. The abstracts of 105 articles were read, and 53 articles were read in full. Finally, 06 articles were considered eligible and included in the review. The cardiometabolic risk factors evaluated in the included studies were body mass index (4 studies), waist-hip ratio (1 study), fat percentage (1 study), blood pressure (2 studies), lipid profile (1 study), inflammatory profile (1 study), and aerobic capacity (3 studies). It is concluded that there is insufficient evidence in the literature about the effect of exercise interventions in PHC with a focus on cardiometabolic risk factors.

Key words: Cardiovascular Diseases; Health; Metabolic Diseases; Physical Activity; Unified Health System.

Resumo – *O objetivo foi buscar sistematicamente e sintetizar as evidências disponíveis na literatura acerca do efeito de intervenções com exercício físico na Atenção Primária à Saúde (APS), realizadas no Brasil, sobre os fatores de risco cardiometabólicos. A busca sistemática foi realizada nas bases de dados PubMed, Biblioteca Virtual em Saúde e Web of Science. Foram incluídos estudos com intervenção de AF ou exercício na APS; realizadas no Brasil; com população >18 anos de idade; pelo menos um fator de risco cardiometabólico avaliado pré e pós intervenção. Utilizou-se o Descritores em Ciências da Saúde para definir os descritores de busca: "physical activity" OR "exercise" OR "motor activity" AND "primary health care" OR "health centers" OR "primary care" AND "Brazil". As fases de seleção foram realizadas por pares e com cegamento e os conflitos decididos por um terceiro avaliador. Utilizou-se a escala de Jadad para avaliar a qualidade metodológica dos artigos incluídos. Foram encontrados 1.817 artigos e excluídas 26 duplicatas, restando 1.791 para leitura dos títulos. Foram lidos 105 resumos e 53 artigos na íntegra. Por fim, 06 artigos foram considerados elegíveis e incluídos na revisão. Os fatores de risco cardiometabólicos avaliados nos estudos incluídos foram índice de massa corporal (4 estudos), razão cintura quadril (1 estudo), percentual de gordura (1 estudo), pressão arterial (2 estudos), perfil lipídico (1 estudo), perfil inflamatório (1 estudo) e capacidade aeróbica (3 estudos). Conclui-se que não há evidências suficientes na literatura sobre o efeito das intervenções de exercícios na APS com foco nos fatores de risco cardiometabólicos.*

Palavras-chave: *Atividade Física; Doenças Cardiovasculares; Doenças Metabólicas; Saúde; Sistema Único de Saúde.*

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INTRODUCTION

Physical inactivity has been the target of major concern by health entities around the world. For example, the World Health Organization (WHO) released a document entitled the "Global action plan on physical activity 2018-2030: more active people for a healthier world" which aims to reduce physical inactivity by 15% by 2030[1]. This concern is based on scientific foundations that show physical inactivity is one of the main factors contributing to global mortality[2]. In addition, it is estimated that between 4 and 5 million deaths in the world could have been avoided if the world population practiced more physical activity (PA)[3,4]. Specifically in Brazil, in 2021, the prevalence of adults (>18-year-old) who did not reach a sufficient PA level was 48.2%[5].

This scenario creates a warning for official bodies, as the physical inactivity prevalence is strongly linked to the development of cardiovascular and metabolic diseases and the increase in cardiometabolic risk factors, such as insulin resistance and type 2 diabetes mellitus[5], arterial hypertension[6], increase in abdominal adiposity, obesity and dyslipidemia, in addition to the increase in the inflammatory state[7,8]. Furthermore, the literature has shown that adults who have a higher aerobic capacity have a lower risk of premature mortality and adverse health-related events. It is noteworthy that this variable is fully interconnected with the regular practice of physical exercise[9]. Thus, it is highlighted that cardiometabolic diseases are the leading cause of death in the world, it is essential to implement public policies and evaluations of PA programs for the control of these diseases worldwide, including in Brazil[10].

The programs that aim to encourage the regular PA practice and physical exercise, especially in the public sphere through the Brazilian Unified Health System (*Sistema Único de Saúde - SUS*), emerge as an important strategy for the metabolic disease prevention and control[11], in addition, to generating lower public health costs in the country[12]. The SUS includes a public policy proposal divided into three levels, primary, secondary, and tertiary health care. Primary Health Care (PHC) is considered the main gateway for users to access the services of the health system and it aims to offer universal access and health promotion program, and actions to prevent disease[13]. Thus, primary care services are focused on prevention and health promotion strategies for the population, aiming at the main determinants of health, including PA.

Thus, understanding and evaluating the characteristics, implementation factors, and results of PA and physical exercise interventions in PHC is an important strategy aid for managers and health professionals, in order to improve the practices involved in this context. In addition, considering that cardiometabolic diseases are the main cause of death in the world[14], PA and exercise programs have been shown to reduce risk factors for these diseases, such as body mass index (BMI), body composition, aerobic capacity, blood pressure (BP), resting heart rate (HR), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), protein C-reactive (CRP), tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), interleukin 10 (IL-10), and blood glucose[15-23].

Thus, the objective of this study was to systematically search and synthesize the evidence available in the literature about the effect of physical exercise interventions Primary Health Care (PHC), carried out in Brazil, on cardiometabolic risk factors.

METHODS

This systematic review followed the PICOS strategy and the methodological recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), proposed by Galvão et al.[24], and is registered on the PROSPERO platform under the number CRD42020209702.

For eligibility criteria, the following inclusion criteria were adopted: a) studies with a PA intervention or physical exercise in PHC; b) studies carried out in Brazil; c) target population over 18 years of age; d) with at least one cardiometabolic risk factor and being evaluated before and after the intervention; e) in English and/or Portuguese; f) published in the last 10 years (January 2010 to September 2020); g) original articles. Exclusion criteria were: a) review (systematic; narrative; integrative and meta-analysis); b) cross-sectional studies; c) theses and monographs; d) abstracts; e) duplicate publications; f) studies with an animal model; g) interventions aimed at assessing mental health status; h) PA intervention or exercise combined with drug therapy, diet, and/or counseling.

The cardiometabolic risk factors considered were: a) factors related to obesity and abdominal adiposity: BMI, waist-hip ratio (WHR), body fat percentage; b) cardiovascular factors: resting and ambulatory BP and HR; c) factors related to insulin resistance: glycemia and fasting or postprandial insulin; d) factors related to dyslipidemia: TC, HDL, LDL, very low-density lipoprotein (VLDL), non-LDL, and TG; e) inflammatory markers: CRP, TNFα, IL-6, IL-10; f) aerobic capacity assessment performed by field or ergometric test.

To find descriptors that would result in the best selection of articles, the Health Sciences Descriptors (DeCS) were used as a strategy for the systematic database search. The databases searched were PubMed, Virtual Health Library (VHL), and Web of Science. For the searches, the following descriptors were used in English: "physical activity" OR "exercise" OR "motor activity" AND "primary health care" OR "health centers" OR "primary care" AND "Brazil". For the PubMed and Web of Science databases, terms with the Boolean operator "NOT" were also added: NOT "review" NOT "systematic review" NOT "cross-sectional study" NOT "cross-sectional" NOT "observational study" NOT "diet". The search was limited to 10 years of scientific production, covering the period from January 2010 to September 2020.

Before starting the selection of studies, which was divided into three phases, duplicate articles were excluded. Subsequently, the first phase was carried out, which consisted of reading the titles and excluding those that met the exclusion criteria (systematic reviews, meta-analysis, cross-sectional studies, studies with an animal model). Next, the abstracts were read and, finally, studies that appeared to meet all the inclusion criteria were read in full. This entire process was carried out using the Rayyan Qatar Computing Research Institute (Rayyan QCRI) software, except for the full reading.

To reduce bias in the studies selection, all selection and eligibility phases were performed by blinded pairs of researchers, through the Rayyan platform, and any conflicts between the pairs were decided by a third evaluator. To extract data from the articles, a pilot form in Microsoft Excel® software (version 2019) was used, by two reviewers, one of whom extracted the information while the other carried out the verification of the extraction. The extraction form contained information on the entire methodology employed by the included study and the main results.

A manual search was performed in the reference lists of the articles included in this review and, after reading the titles of all references, 24 articles were selected for full reading, however, none of them met the inclusion criteria for this study. The criteria considered for this search were studies with the terms "PHC", "physical exercise", or "physical activity" contained in the title and that were considered as a potential article for inclusion in the review.

The methodological quality of the included studies was assessed by two reviewers, and, in case of disagreement, a third reviewer was consulted in order to reach a consensus. To analyze the methodological quality of the included articles, the Jadad scale was used, which contains a list of five questions that assess three different aspects of clinical trials: randomization, blinding, and description of losses and exclusions from the study, resulting in a score that can range from 0 to 5. Studies with scores below 3 were considered to present a high risk of bias[25]. The scale questions are: A= Was the study described as randomized? B= Has the method for generating the randomization sequence been described and is it appropriate? C= Was the study described as double-blind? D= Has the double-blind method been described and is it appropriate? E= Was there a description of exclusions and dropouts following the study?

RESULTS

In total, 1,817 articles were found (PubMed: 609; VHL: 56; Web of Science: 1,152). Twenty-six duplicate articles were excluded, totaling 1,791 for reading the titles. Of these, 1,686 were excluded and 105 articles remained for reading the abstracts. Of these, 3 were excluded for not being performed in Brazil, 39 for not presenting a PA or exercise intervention, or not being performed in PHC, 1 for not including the target age group, 6 for presenting a PA intervention or exercise combined with drug therapy or diet, and 3 for being a review, thesis, or congress abstract. For the third phase, 53 articles were selected for full reading, of these, 1 was excluded for not being performed in Brazil, 36 for not presenting a PA or exercise intervention or not being performed in PHC, 1 for not including the target age group, 7 for not considering at least one of the stipulated cardiometabolic risk factors, 1 for presenting a PA intervention or exercise combined with drug therapy or diet, and 1 transversal study. At the end of the process described, 06 articles met the inclusion criteria and were selected for this review. Figure 1 shows the study search process, and the results and reasons for exclusion from the abstract to the full reading phase.

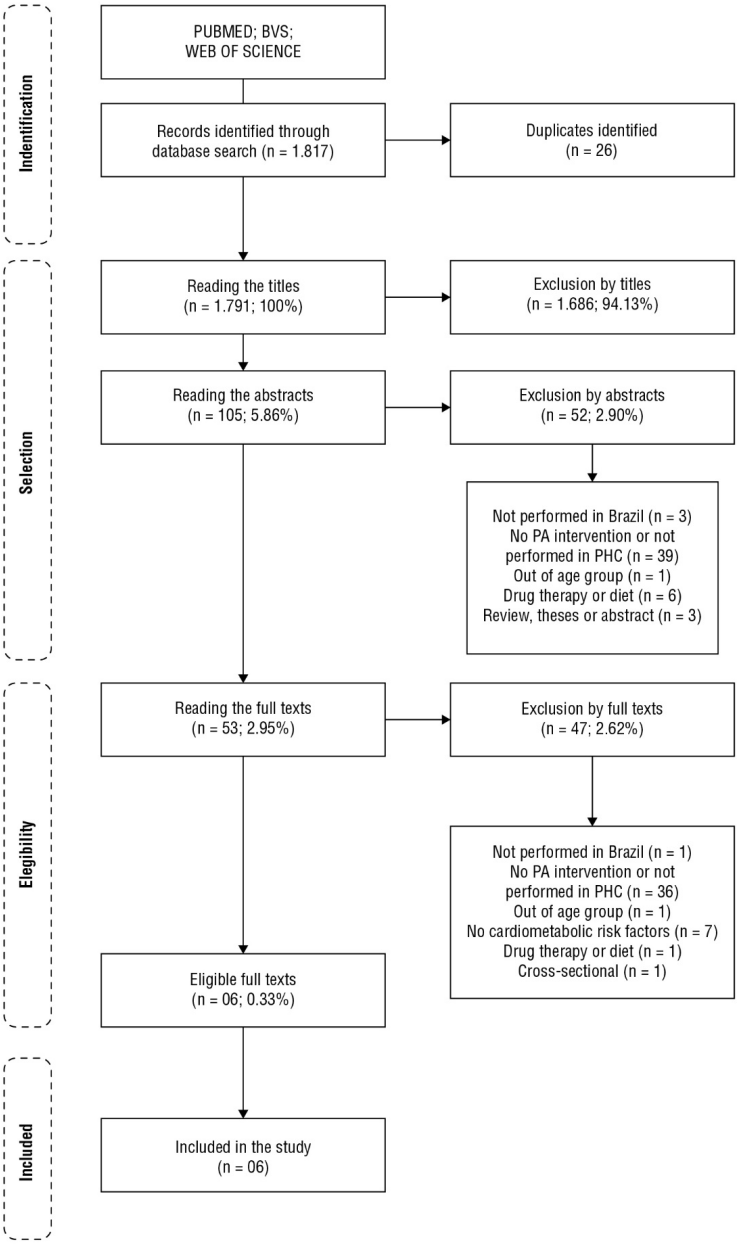

Figure 1. Flowchart of identification, selection and reasons for excluding articles

Table 1 presents the analysis of the methodological quality of the articles included in this review, according to the Jadad scale[25].

Table 1. Methodological quality analysis of the articles included (Jadad scale[25]).

Studies	Question Scores					Final Score
	A	B	C	D	E	
Benedetti et al.[26] 2020	1	0	0	0	1	2
da Cunha et al.[17] 2010	1	0	0	0	1	2
Lima et al.[19] 2019	0	0	0	0	1	1
Nakamura et al.[27] 2015	0	0	0	0	1	1
Papini et al.[20] 2014	0	0	0	0	1	1
Vianna et al.[28] 2012	1	1	0	0	1	3

Table 2 presents the characteristics of the original articles included in the review. Study samples varied in terms of location, sample size, age, and groups. For the groups that underwent a physical exercise intervention for which the data were extracted for this review, a common terminology was adopted EG for Exercise Group. For the other groups, the same terminology indicated by the authors of the included studies was used, although these data were not extracted, as they are not the focus of this review.

Table 2. Characterization of included studies.

Author, year	Location	Sample	Age (average or range)	Groups
Benedetti et al.[26] 2020	Florianopolis (SC)	Outset=114 3 months=74	> 60	*Outset:* EG=52, CG=26; BCG=36; *3 months:* EG=33, CG= 23, BCG=18
da Cunha et al.[17] 2010	Juazeiro do Norte (CE)	n=98	> 60	EG=58, CG=40
Lima et al.[19] 2019	Rio de Janeiro (RJ)	Outset =182 12 months=144	30 to 74	*Outset:* EG=86, DAG=48, PIG= 348 *12 months:* EG=53, DAG=43, PIG=48
Nakamura et al.[27] 2015	Rio Claro (SP)	n=440	> 20	EG=440
Papini et al.[20] 2014	Rio Claro (SP)	Outset =36 12 months=13	56.8±11.4	*Outset:* EG=36 *12 months:* EG=13
Vianna et al.[28] 2012	Santa Cruz de Minas (MG)	n=70	EG:68.6±5.9 CG:69.8±8.05	EG=35 CG=35

Note. EG: Exercise Group; CG Control Group; BCG: Behavior Change Group; DAG: Declared Active Group; PIG: Physically Inactive Group; SC: Santa Catarina; CE: Ceará; RJ: Rio de Janeiro; SP: São Paulo; MG: Minas Gerais.

Table 3 presents the methodology characteristics used in the physical exercise interventions in the studies included in this review, as well as the results obtained by these exercise interventions, through the cardiometabolic risk factors considered, and the significant effects of the interventions (improvement, worsening, or maintenance).

Table 3. Characteristics of the interventions of the included studies.

Author, year	Time	Sessions x Duration	Type of exercise	Intensity	Results
Benedetti et al.[26] 2020	3 months	3x/week 60 min	Aerobic and resistance	50-80% of Max Aerobic Power	BMI = **o**
da Cunha et al.[17] 2010	4 months	3x/week 45 min	Walking and stretching	55-75% of Max HR	BMI = **+** % Fat = **o** Aerobic C. = **+**
Lima et al.[19] 2019	12 months	3x/week 30-60 min	Aerobic, strength, stretching, and walking	Range from light to vigorous Light (Borg 1-3) Moderate (Borg 5-6) Vigorous (Borg 7-8)	SBP = **+** DBP = **+** TC = **+** LDL = **+** HDL = **o** TG = **+**

Note. HR: heart rate; Max: maximum; SPE: subjective perception of effort; min: minutes; (**+**): improvement; (**-**): worsens; (**o**): maintenance; BMI: body mass index; WHR: waist-to-hip ratio; Aerobic C.: aerobic capacity; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; IL10: interleukin 10; IL6: interleukin 6; TNFα: tumor necrosis factor alpha. Note: for the effects of the intervention, statistically significant results were considered.

Table 3. Continued...

Author, year	Time	Sessions x Duration	Type of exercise	Intensity	Results
Nakamura et al.[27] 2015	10 years	2x/week 60 min	Aerobic, strength, flexibility, agility, coordination, balance, stretching and walking	Moderate Intensity	Aerobic C. = +
Papini et al.[20] 2014	12 months	2x/week 60 min	Aerobic, strength, stretching and walking	Walking: moderate (60-70% of HR peak and SPE between 13-15 points)	BMI = 0 WHR = 0 CRP = + TNFα = + IL6 = 0 IL10 = 0 Insulin = 0
Vianna et al.[28] 2012	4 months	3x/week 60 min	Water aerobics, weight-training, walking and stretching	Aerobic: moderate (55-65% of Max HR and SPE between 12-13 points) Flexibility: PERFLEX (31-60: normal)	BMI = 0 SBP = 0 DBP = - Aerobic C. = +

Note. HR: heart rate; Max: maximum; SPE: subjective perception of effort; min: minutes; (+): improvement; (-): worsens; (0): maintenance; BMI: body mass index; WHR: waist-to-hip ratio; Aerobic C.: aerobic capacity; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; IL10: interleukin 10; IL6: interleukin 6; TNFα: tumor necrosis factor alpha. Note: for the effects of the intervention, statistically significant results were considered.

The intervention time ranged from 3 months to 10 years, the sessions were performed between 2 and 3 times a week, and the duration was between 30 and 60 minutes. Regarding the type of exercise offered, aerobic and resistance (strength) exercises were the most prevalent, followed by stretching. Different intensities and measures were considered; however, the moderate intensity was the most frequent.

Although other cardiometabolic risk factors were considered for the selection of studies, such as factors related to insulin resistance, no studies were found that evaluated these variables.

DISCUSSION

Physical inactivity is a major problem for public health and an important risk factor for cardiovascular and metabolic disease. As a result, concerns about the subject have become recurrent, encouraging the evaluation of interventions with exercise and PA in the public health system[3,29]. Thus, the aim of the current systematic review was to systematically search and synthesize the evidence available in the literature about the effect of physical exercise interventions in PHC, carried out in Brazil, on cardiometabolic risk factors. Through the search strategy used, 06 articles were selected for the review, demonstrating the lack of studies in Brazil with physical exercise interventions in PHC focusing on cardiovascular health. Consequently, the evidence regarding the effect of the interventions is inconclusive.

The population studied in this study varied from adults to older adults. The study interventions lasted from 3 months to 10 years, with a frequency of 2 to 3 times a week, sessions of 30 to 60 minutes, and a prevalence of aerobic,

resistance (strength) and stretching exercises, however, some interventions also adopted flexibility exercises, coordination, balance, agility[27], and water aerobics[28]. The frequencies and durations of the sessions are the most commonly adopted in interventions carried out in public health contexts, as well as the types of exercise used, as they are easy to apply, using materials such as brooms and plastic bottles for resistance training and walking for aerobic workouts.

Several methods were used to control intensity in the included studies, such as percentage range of maximum aerobic power[26], maximum HR[17,28], peak HR[20], rate of subjective perceived exertion scales[19,20,28], an HR monitor[20], and an exercise flexibility scale[28].

The cardiometabolic risk factors evaluated in the included articles were BMI[17,20,26,28], WHR [20], aerobic capacity[17,27,28], body composition[17], lipid metabolism[19], glucose metabolism[20], inflammatory markers[20], and resting BP[19,28]. It is noteworthy that the evaluation of the variables BMI, WHR, aerobic capacity, body composition, and BP are easily accessible and, thus, these variables are widely used in public health interventions, particularly considering the difficulty of performing more robust assessments in these contexts. More robust evaluation methods were used only to obtain the lipid profile and inflammatory markers, which were performed using laboratory tests.

Considering the main results of this review, the improvement in aerobic capacity stands out in the 3 studies that evaluated this parameter, after 4 months[17,28] and 10 years[27] of intervention. Aerobic capacity was assessed by indirect methods in the 3 studies, such as the WT6 walk test[17], 1600-meter walk test[28], and AAHPERD's walking test[27]. It should be noted that indirect measures may lead to some limitations in the results of the studies.

Four studies in this review assessed BMI, however, only one showed improvement in this parameter after 4 months[17], while the others showed maintenance of its values after 3 months[26], 12 months[20], and 4 months[28] of intervention. A systematic review and meta-analysis evaluated the effect of physical exercise on anthropometric measures, with studies longer than 3 months of intervention, showed that aerobic and resistance exercise of moderate to vigorous intensity significantly reduced the BMI of participants in the included studies[30]. It is noteworthy that diet was not controlled in any of the studies included in this review. Of the studies included and cited for BMI, only the control group for the intervention by da Cunha et al.[17] presented worsening in the results. These data become relevant and need attention, as obesity can directly contribute to the incidence of cardiometabolic risk factors, such as dyslipidemia, type 2 diabetes mellitus and arterial hypertension, in addition to leading to the development and mortality from diseases cardiovascular diseases, regardless of other cardiometabolic risk factors[31].

BP was evaluated in two studies. In the study by Lima et al.[19] there was an improvement in systolic and diastolic BP after 12 months of follow-up. However, in the study by Vianna et al.[28], after 4 months of intervention, there was the maintenance of systolic BP and worsening of diastolic BP. Due to the low number of studies included and considering the synthesis of results, there is no evidence that interventions with physical exercise in PHC improve BP. Considering that both studies applied aerobic and resistance exercises in their interventions, a systematic review conducted by Rocha et al.[32] found that combined training induced BP reductions. The duration of the intervention in the study by Vianna et al.[28] may have influenced the BP result (maintenance in

systolic and worsening in diastolic). A study that aimed to investigate whether post-exercise hypotension remains constant in hypertensive older women who do not use medication, found that BP was reduced after an acute session of moderate-intensity exercise, however, the acute hypotensive effect did not occur after 12 weeks of training[33].

The lipid profile was evaluated by Lima et al.[19] and showed improvement in TC, LDL, and TG, as well as maintenance in HDL after 12 months of intervention for the group that practiced supervised exercise, and worsening in TC, LDL, and TG for the group considered physically inactive. The inflammatory profile was analyzed by Papini et al.[20], showing improvements in CRP and TNFα and maintenance in IL-6, IL-10, and insulin. However, considering the low methodological quality of the included studies and the lack of other studies, it is not possible to confirm the evidence of the effect of physical exercise offered in PHC on these parameters.

Among included studies, 01 was carried out in Santa Catarina, 01 in Ceará, 01 in Rio de Janeiro, 02 in São Paulo, and 01 in Minas Gerais, demonstrating a higher prevalence of this type of study in the Southeast region of Brazil. A similar result was found in a systematic review carried out by Becker et al.[34], in which the authors justify this prevalence by the greater concentration of researchers, research centers, and postgraduate courses in the Southeast region.

Regarding the analysis of the methodological quality of the included studies, performed using the Jadad scale[25], it was observed that most studies scored less than three points, indicating a high risk of bias in the methodology. The only study that obtained a score equal to three was by Vianna et al.[28], highlighting the need for more robust studies, particularly randomized trials, focusing on the provision of physical exercise for the adult and older populations in PHC. However, there is difficulty in carrying out randomized studies in the context of PHC, especially considering the lack of records of users of health units, in addition to the difficulty in making contact using existing records (refusal to participate, wrong or non-existent telephone contacts), making it impossible to create a list of individuals for randomization.

Taking into account that the characteristics of the Brazilian health system (i.e. universal and free access to health actions and acting to reduce social disparity) provide several opportunities for the development of actions to promote health through the practice of physical exercise[35], the findings of this systematic review could encourage the implementation of more physical exercise interventions in PHC and raise an alert about the absence of studies carried out in PHC focusing on the cardiovascular health of users. In addition, the evidence shown here could contribute to public policies and the actions of health managers in Brazil. However, some issues need to be better investigated, especially the barriers to the implementation of these programs, such as factors of adherence of the target audience, bureaucratic actions, organizational structure, and the population's lack of knowledge regarding the inclusion of PA in PHC, reflecting, thus, the reality of PA and exercise interventions in PHC.

This review has some limitations, and we can highlight the methodological quality of the included studies, since five of the six articles included presented a high risk of bias and, of these, most did not present the randomization sequence method and did not describe the study as double-blind, in addition to the number of databases searched and the limited search period. However, as the strengths of this review, it is noteworthy that the articles were published in important

peer-reviewed journals, in addition to the presentation of the methodological quality, the phases carried out by pairs and with blinding, and the preparation of spreadsheets to ensure data extraction quality and for conflict analysis.

CONCLUSION

It is concluded that there is insufficient evidence in the literature about the effect of physical exercise interventions in PHC carried out in Brazil, with a focus on cardiometabolic risk factors that were considered for this review. Furthermore, the studies included in this review present limitations in the methodologies used, therefore, there is a need for further studies on the subject, particularly controlled, randomized, and with less methodological bias.

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical approval

This research is in accordance with the standards set by the Declaration of Helsinki.

Conflict of interest statement

The authors have no conflict of interests to declare.

Author Contributions

Conceived and designed the experiments: KAB, BTGB, AFACS, GLC, RBFV, LFB, CBP; Performed the experiments: KAB, BTGB, AFACS, GLC, RBFV, LFB, CBP; Analyzed the data: KAB, CBP; Wrote the paper: KAB, CBP; Critical analysis: KAB, BTGB, AFACS, GLC, RBFV, LFB, ACRA, GMP, CBP.

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