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EFFECTS OF THE PHYSICAL EXERCISE ON THE COGNITIVE FUNCTION AND ON THE MOOD

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Abstract

In our overview of systematic reviews (SRs) we explored the effects of the physical exercise (PE) on both together the cognitive function (CF) and the mood by SRs of randomized and controlled trials (RCTs). We found SRs exploring different conditions: obesity and overweight in children and adolescents, stroke adult survivors, elderly mild cognitive impairment (MCI) and dementia. In practice, we selected in PubMed 4 SRs of RCTs with an intervention time median range of 2-24 months. We assessed the risk of bias in the SRs with the Assessment of Multiple Systematic Reviews (AMSTAR) tool. As concerns the results, about dementia and MCI in elderly patients one SR observed a positive effect of PE and cognitive intervention only on the global cognitive function (GCF). Another SR on elderly people in nursing homes found a significant effect only by the multimodal type of PE. A secondary concomitant effect has been observed also on the mood in both the SRs. A SR on overweight or obese children and adolescents registered a good effect of only PE (without concomitant diet or lifestyle education) on the cognitive executive functions. As concerns adult stroke survivors, where mood and CF were considered both as secondary outcomes in a very few primary studies, a moderate effect of strength exercises was registered on mood, while cardiorespiratory exercises resulted effective in physical fitness present as primary outcome in a very larger number of studies. The overall risk of bias in the SRs here examined was low or moderate. All the primary researches in every SR were affected by a high degree of heterogeneity between studies, due to a large variety of measurement tools, of duration and frequency of the sessions, of treatment and follow-up duration. In the future, larger trials with higher number of covariates and more homogeneous measurement tools with their relative outcomes are needed in order to obtain a more detailed information and results.

Key words: *physical exercise, cognitive function, mood, randomized controlled trials, systematic reviews, heterogeneity, and risk of bias.*

Introduction

Physical exercise (PE) is recommended to the general population by many medical entities – including the Centers for Disease Control and Prevention and the American College of Sports Medicine – because it is considered an important tool for the improvement of public health. As is the case for non-psychiatric diseases, physical activity might be an effective measure for the treatment and even for the prevention of psychiatric diseases such as depressive and anxiety disorders. In addition, PE has increasingly been recommended to individuals with or without disease in order to improve their quality of life. On the other hand, PE can compromise mental health, especially when performed in a more intense manner (1). Furthermore, chronic diseases are long-term conditions with slow disease progression and without an effective cure, and, e.g., from China death registers (2) it results that 38 million people die there from chronic diseases each year. In addition, 16 million of these deaths occur before the age of 70 years. Chronic diseases may lead to alteration in brain structure and function and are associated with cognitive change. Some of these changes may be related to neurodegenerative diseases (such as Alzheimer's disease and other types of dementia), increased dementia incidence, and cognitive decline. Strategies are needed to reduce disease-related cognitive impairment in chronic disease patients. Exercise, the aim of which is to improve or maintain physical fitness, is a subset of physical activity that is planned, structured, and flexible, in addition to promoting aerobic endurance. Exercise is essential in maintaining physical function and physiological health. The results of animal studies have identified that engagement in physical activity may enhance neurotrophic factor levels, neurogenesis and vascularization, and may even reduce aggregation of pathogenic proteins, mediate neuroinflammation, and inhibit neuronal dysfunction. Exercise also appears to be associated with the maintenance of brain health and cognitive performance in cognitively normal older adults. Most experimental studies have identified increased lifetime physical activity to be associated with reduced risk of suffering from dementia in cognitively normal older persons (2). Moreover, also the prevalence of overweight and obesity in children in the United States is currently 31%. Specifically, the prevalence of obesity has increased from 13.7% of children and 11.5% of adolescents in the 1988–1994 period to 17.1% of children and adolescents by the year 2010. Moreover, research shows that overweight children are more likely to remain overweight as adults. These alarming statistics support the necessity for effective interventions to target obesity in children, and to look beyond basic nutrition and physical activity recommendations. Neurocognitive functioning, which influences cognitions, emotions, and behaviors linked to obesity, may be an important, yet under-emphasized factor, in informing existing and future weight-loss interventions. Limited research has emerged examining differences in neurocognitive functioning between obese versus non-obese youth; only a few studies have explored how neurocognitive factors relate to behaviors that promote weight gain. Obesity-related behaviors, such as food intake and physical activity, may play a role in the relationship between neurocognitive functioning and weight (3).

In this overview of systematic reviews (SRs) relative to the effect of PE on cognitive function (CF) and mood, our objective has been to assess the actual degree of evidence of this relationship in every pathological or pre-pathological conditions described by randomized and controlled trials (RCTs) in the literature. This, in order to evaluate the different impact of PE on cognitive function (CF) and mood in settings differing each other by age, pathology and intervention type. Being very high the number of the published primary studies, we have considered less time-consuming and more exhaustive to take into consideration and to select and evaluate only the SRs of primary studies relative to our objective of research.

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Methods

Search strategy

In May 2019 systematic search was conducted in the database PubMed. We used the terms "physical exercise AND cognitive function AND mood" using the following filters: article types: *reviews*; publication dates: 5 *years* before 2019; species: *humans*. To identify eventual additional potentially relevant articles, the reference lists of the selected articles were screened.

Eligibility criteria and study selection

Studies were eligible if they met the following inclusion criteria: 1) only SRs (qualitative or quantitative); 2) SRs considering as primary studies only randomized and controlled clinical trials (RCTs) or cluster RCTs (cRCTs); 3) only SRs including primary studies relative to the effect of PE on *both* CF and mood. The reviews were excluded if they were reviews of: 1) prospective or retrospective cohort studies; 2) cross-sectional studies; 3) case-control studies. If different reviews would include the same primary study, a sensitivity analysis - testing the kind of results obtained including and excluding this duplicated study in the whole context of the reviews – was done. Two reviewers screened the title/abstracts and subsequently full text articles separately. Eventual disagreements were planned to be discussed with a third researcher and subsequently adjusted after reaching consensus.

Interventions and outcome measures

Only RCTs with PE intervention group, that also included an active or passive control group, were included. Global and specific cognitive and mood functions, evaluated with validated screening tools, were used as the outcome measures. Other outcome measures were performance on the domains of memory, attention and activities of daily living (ADL). All outcome measures had to be determined at baseline and directly after the intervention period.

Risk of bias assessment

The measurement tool for the "assessment of multiple systematic reviews" (AMSTAR) - developed by Shea et al. and successively validated (4) – for assessing risk of bias in SRs, was used as a measure of quality assessment (Table 1). Each bias domain was rated as low (yes) or high or unclear (no) (Table 2). The final judgment for each SR was of low risk of bias if the affirmative answers to the 11 items in Table 1 were at least 9/11; moderate if they were 5-8/11; high if there were less than 5/11 affirmative answers. Two researchers independently performed the risk of bias assessment. Eventual differences that we found in outcome were planned to be discussed with a third researcher until consensus was reached. A total risk of bias judgment was based on the assessment of all domains.

Analysis

The SRs we have recruited were one qualitative SR and three quantitative SRs. Because of the high degree of heterogeneity between primary studies registered in the SRs (5-8), a subgroup analysis – to assess eventual differences between subgroups by the available covariates - was not successful also for the quantitative SRs (6-8).

Results

Identification of studies and risk of bias assessment

The Figure shows the flow diagram of the SRs selection in our overview. The initial search yielded 91 reviews (published between January 2014 and December 2018). Based on titles and abstracts 81 papers were excluded. The remaining 10 articles were screened full text, leading to exclusion of six articles.

Table 2 shows the risk-of-bias profile for the four included SRs. The final judgment was of low risk in (6), (7) and (8); it was of moderate risk of bias in (5). There was an inclusion bias in SRs (5) and (8) (they considered only primary studies published in English; also, (8) has excluded conference abstracts). The publication bias was not assessed in (5) (6) (7) relative to the mood and cognitive function outcomes. Finally, the conflict of interest was not declared from (5) and (8).

Participants and study characteristics

Table 3 summarizes the characteristics and the outcomes of the included RCTs and cluster RCTs (cRCTs), review by review. They are all open and pertain to different pre-pathologic or pathologic conditions. Two of the four SRs were relative to primary studies on dementia and MCI in elderly people (5) (8) (number of primary studies, respectively: 12 and 10; global sample sizes: 901 and 742). One SR was on stroke survivors (7) (number of primary studies: 58; global sample size: 2707), and one on obese children and adolescents (number of primary studies: 18; global sample size: 2384). Three SRs collected elderly or middle-aged people (5) (7) (8) .Two SRs (5) (8) were relative to a disabling pathology (dementia or MCI) and one SR to a reversible pathologic condition (stroke survivors followed in an ambulatory setting) (7)). Another SR (6) collected primary studies on children and adolescents subjected to a pre-pathological condition (obesity). All reviews consisted of a PE intervention in various forms, alone (Brett (5), Saunders (7) or combined with cognitive (Karssemeijer (8)) or lifestyle educational or diet (Martin (6)) interventions. The combination PE-cognitive intervention in (8) was unique for all patients, while different types of physical interventions in (5-7) (Table 3) were assigned to groups of patients independent from each other. The training frequency varied from 1 to 6 sessions per week and the duration per session varied from 15 to 300 min. The different types of exercise interventions are indicated in the Table 3. The used outcome measurement tools in the different studies varied widely between studies not only in dependence of the specific disease, but likewise inside each specific pathology. The more diffused measurement tools in the geriatric context were the Mini-Mental State examination (MMSE), the Alzheimer Disease Assessment Scale- Cognitive subscale (ADAS-Cog), the Nurse Observation Scale for Geriatric patients (NOSGER) and the Geriatric Depression Scale (GDS). For the academic children and adolescent's achievement, the more diffused scales were the Grade Point Average (GPA) or the Canadian Achievement Test (CAT)-3.

Primary and secondary analysis

The outcome analysis was quantitative in tree of the four reviews included (6) (7) (8). Nevertheless, in two of them (6) (7) the high degree of the outcome heterogeneity prevented a synthetic plausible quantitative answer and likewise the subgroup analysis was ineffective. Therefore, we have often knowledge of the positive and negative results but it was not possible to determine precisely the effect degree (low, moderate or strong). Obviously, particularly in the qualitative SR (5), the heterogeneity is heavier and the precision is weaker. The Brett (5) and the Martin (6) SRs included both RCTs and cluster RCTs. In every RCT, the randomization was open.

In their SR on dementia and MCI in elderly subjects (mean age 71 years), Karssemeijer et al. (8) found a low risk of bias in 6/10 studies. Concerning the *primary outcomes*, they found small-to-medium effect of the combined PE-cognitive intervention only on the *global* cognitive function (GCF) (10 primary studies, 742 subjects), here finding also no heterogeneity between studies and no publication bias using the funnel plot graph analysis. Furthermore, they found not significant the intervention on specific skills (memory, verbal, spatial orientation, etc.). As concerns the *secondary effects,* they only found: 1) a medium-large effect of the intervention on the activities of daily living (ADL) (but here they found 80% of heterogeneity between studies), 2) a small-medium effect on the mood (no heterogeneity between primary studies, no evidence of publication bias).

In their SR on very elderly subjects with dementia assisted in nursing homes (mean age 83 years), Brett et al. (5) sub-grouped the patients in the primary studies by different PE types of *primary intervention* (multimodal, music and movement, hand exercises) and they found significance only in the multimodal group. The *secondary intervention* was on the mood, and here too only the multimodal subgroup intervention resulted significant. Risk of bias in the primary studies resulted low in nine studies, medium in three studies. The patient's attendance in the primary studies presented a very wide range (33-100%).

In their SR on stroke elderly-middle aged survivors, Saunders et al. (7) also sub-grouped the subjects in the primary studies by type of PE (cardiorespiratory, strength and mixed), but both mood and CF were only considered as secondary outcomes. Mood improvement resulted significant only in the strength subgroup; CF resulted not significant. However, these secondary outcomes were assessed in a few number of studies (respectively, two and three trials). The mean age of the subjects was 62 years. The overall risk of bias in the primary studies resulted moderate. The patient's attendance in the primary studies presented a wide range (65-100%).

In their SR on obese and overweight children and adolescents (3-18 years of age, 10 different countries), Martin et al. sub-grouped the subjects in the primary studies by treatment as follows: PE alone, PE + lifestyle education, PE + diet administered. The overall risk of bias in the primary studies resulted moderate. The primary outcomes were the following: school achievement, cognitive function, adverse events in PE. Only in the subgroup with only PE there was an improvement, specifically in cognitive executive functions (that are, mental control and self-regulation). The subject's attendance in the primary studies presented an acceptable range (71-100%).

Discussion and conclusions

Interpretation of results

Our overview examined the most recent synthetic findings of SRs – relative to RCTs and cRCTs as primary studies - on the role of PE on the CF and mood in a wide range of pre-pathological and pathological conditions. The interventions considered were of primary prevention (in overweight and obesity of scholar children and adolescents), secondary prevention (in ambulatory adults stroke survivors), and rehabilitation (in elderly subjects with MCI or dementia). Four SRs published between 2016 and 2018 were included in our overview.

Only in the primary prevention setting of overweight or obese young people in scholar age, the PE is not supporting a medical therapy and is the only determinant of the effect measurement. Here resulted a good effect of PE alone only on cognitive executive functions, while PE + (lifestyle education *or* diet) resulted here not significant. Despite the high primary studies heterogeneity that prevented a definition of the effects more complete and detailed, it appears evident that in younger subjects PE promotes the self-control that is an important achievement at school attendance. In this setting, depression is included in the context of the adverse events that were globally not significant. Probably, in obese and overweight children and adolescents, obesity has not considered a consequence or a cause of a depressed mood but rather of a wrong parental lifestyle or education. Therefore, the depressive mood was not considered important. This dependence from their parents in the children lifestyles could be also the reason of the ineffective lifestyle education and diet associated to the PE. In fact, here the parents were not involved.

In the rehabilitation setting of MCI or dementia in elderly people, as in the primary prevention setting above described, the CF was considered a primary outcome. Differently from the primary prevention setting (6), here PE integrates the medical therapy. Karssemeijer et al. (8) found a small-medium effect of PE and cognitive intervention only on the global cognitive function (GCF) and Brett et al. found a significant effect (not quantified) of PE only on

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the multimodal type of PE group. Probably, the efficacy on the GCF and of the multimodal PE intervention were successful mainly because they were various as are the usual activities in the everyday life. The mood here was registered as a secondary outcome. This, probably because the SRs authors considered a mood improvement as natural effect of the intervention on the primary outcomes. This hypothesis appears to be likely in both cases: the mood registers – like GCF - a small to medium effect in (8) and is significant – like PE - only in the multimodal group in (5).

In the secondary prevention setting of ambulatory stroke survivors (7), the primary studies focus is on the physical outcomes. Not only mood and CF are registered in the Saunders et al. SR as secondary outcomes, but they are considered, respectively, in only two and three primary studies. Nevertheless, mood has resulted moderately significant in the strength group of PE. It resulted not significant in the cardiorespiratory and mixed (cardiorespiratory-strength) groups. The lower consideration of CF and mood is likely related to the normal or quite-normal gait of these subjects referring to an ambulatory set, that emphasizes in the caregivers the need of preventing future cerebrovascular obstructions and physical disabilities, given that the stroke in those subjects with transitory ischemic attack generally did not yet seriously compromise the neurological functions.

Strenght and limitations of this overview

A strength of this overview is that only SRs on RCT or cRCT primary studies were included. cRCT design randomization is a little more prone to bias than an RCT design, but only a few cRCT groups were included in some of the SRs here considered. It is sufficiently clear that an educational lifestyle program should be addressed also to the parents of the children and adolescents to be practically effected, and that PE in the youngest people is effective in promoting characteristics of self-control and task-concentration (executive cognitive functions). Furthermore, it appears clear that diversified PEs that had better promoted the different activities of the everyday life is more interesting – and therefore successful – than more specialized and monotonous exercises for the ancient people in conditions of MCI or dementia (Table 3). There are also limitations that need to be addressed when interpreting the results. First, there is considerable heterogeneity in the primary studies regarding the intervention characteristics (e.g., type of training, separate or multiple-tasks, intervention period, frequency, duration) and the measurement tools used (MMSE, ADAS-cog, AMS, NOSGER, GPA, CAT-3, etc.). Therefore, the optimal PEs intervention design, for eliciting beneficial effects, remains in all the SRs unclear. Due to the high methodological heterogeneity it was no possible to analyze the impact of different intervention components or to calculate the efficacy for different conditions of disease severity using a subgroup (subgrouping by 'moderator' covariates) analysis. However, subgroup quantitative meta-analyses are very useful in developing preventive strategies and designing appropriate interventions. Second, the adherence of the enrolled subjects to the interventions and the intensity of the PE program was not reported in detail in several primary studies, which could have influenced also the SRs results. In addition, data about adherence and intensity of intervention programs are essential to gain insight in dose-response ratios. Finally, in two SRs of four, only studies reported in English were included and, furthermore, the conflict of interest was not stated.

Implications for future research

To investigate the different intervention combinations, we need future research. For adult or elderly people with MCI, dementia or cardiovascular diseases we suggest a multi-arm design, including a cognitive, nutritional (9) and physical training, single physical training, single cognitive training, single nutritional training and a control group to distinguish the contribution of different components of the intervention.

Furthermore, additional studies should explore the most effective training characteristics in combined interventions specifically aiming at duration, frequency, intervention type and mode of combination. Moreover, in secondary and tertiary prevention studies future research should focus on investigating physiologic mechanisms that underlie the positive effect by including neuroimaging measures and molecular markers as an outcome. In addition, long-term effects of combined interventions could in future gain insight into possible maintenance effects. Finally, the identification of individual predictors for a beneficial outcome (i.e., using individual patient data meta-analyses) is also important to personalize multi-modal interventions. Conversely, in young people the interventions focusing on one target behavior, i.e. PE, our findings suggest that they yield beneficial effects on cognitive executive functions and, consequently, also on memory and general intelligence compared to standard practice. In childhood and adolescence, it might be that the positive effect of the PE program on the cognitive functions is diluted with the increasing complexity of the interventions. The intensity of the PE component at this early age might be reduced when additional intervention activities, such healthy lifestyle education sessions, are implemented. Moreover, healthy lifestyle and diet education is here probably a parental issue. To conclude, selecting with standardized univocal methods appropriate outcome measurements in larger studies is essential in future research.

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TABLE 1 - AMSTAR measurement tool assessing the methodological quality of systematic reviews.

1 – Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.
2 – Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3 – Was a comprehensive literature search performed? At least two electronic sources should be searched. Fhe report must include years and databases used (e.g. Central, Embase, and MEDLINE). Key words and/or MESH terms should be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and bt)
4 – Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
5 – Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.
6 – Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age,race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
7 – Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the authors chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
8 – Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodologic rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
9 – Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable , to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. Is it sensible to combine?).
10 – Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, oter available tests) and/or statistical tests (e.g., Egger regression test).
11 – Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Table 2 – Risk of bias assessment per AMSTAR domain across studies.

Author	Karssmeijer	Brett	Saunders	Martin
1-design	yes	yes	yes	yes
2-selection	yes	yes	yes	yes
3-search	yes	yes	yes	yes
4-inclusion	no	no	yes	yes
5-checklist	yes	yes	yes	yes
6-characteristics	yes	yes	yes	yes
7-quality	yes	yes	yes	yes
8-conclusions	yes	yes	yes	yes
9-methods	yes	yes	yes	yes
10-publication	yes	no	no	no
11-conflict	no	no	yes	yes

Table 3 – SRs characteristics

First author	Karssemeijer	Brett	Saunders	Martin
Type of SR	Quantitative	Qualitative	Quantitative	Quantitative
N. (studies/subjects)	10/742	12/901	58/2707	18/2324
Study design	RCTs open	RCTs, cRCTs open	RCTs open	RCTs, cRCTs open
Disease	dementia, MCI	dementia	stroke survivors	obesity, overweight
Setting	nr	nursing homes	ambulatory	schools in 10 countries
Mean age	71years	82.6years	62years	3-18years
Male gender	41%	nr	nr	nr
Intervention	PE, cognitive	PE (multimodal, hand, walk, music)	PE (aerobic, anaerobic, mixed)	PE, PE+ education, PE+ diet
Control treatment	usual therapy	usual therapy	usual therapy	usual
Intervention tools	MMSE, ADAS-cog et al.	MMSE, AMS, NOSGER et al.	various rating scales	GPA, CAT-3 et al.
RoB in primary studies	low(6),unclear(4)	low(9)medium(3)	moderate	moderate
Treatm. Duration (range of weeks)	8-52	4-52	8-16	24-76
Session duration/ /frequency(range)	30-300min/ /1-5 x week	15-120/ /2-6 x week	20-180 min/ /2-5 x week	15-60 min/ /2-5 x week
Primary outcomes	verbal, memory, spatial orientation, GCF	Multimodal, music, walk	ADL, disability, death, mobility, phys. fitness	school achievement, cognitive function, adverse events
Secondary outcomes	ADL, mood	mood	mood, CF	future success, obesity
Primary effects/ /heterogeneity	GCF: small-medium/ 0%; others: ns	signif. in multimodal /0%; others: ns		good of PE on cognitive executive functions/high
Second. effects/ /heterogeneity	ADL: medium-large/ /80%; mood: small-medium/0%	signif.in multimodal and walking group/ nr	mood moderately signif.in anaerobic groups/nr	discordant/high
Attendance	nr	33-100% (5 of 12 studies)	65-100%	71-100%
Publication bias	absent	nr	nr	nr

Key: ADAS-Cog=Alzheimer Disease Assessment Scale-Cognitive subscale; ADL=Activities of Daily Living; AMS=Alzheimer Mood Scale; CAT-3=Canadian Achievement Test (third version); GCF=Global Cognitive Function; GPA=Grade Point Average; MMSE=Mini-Mental State Examination; NOSGER=Nurse Observation Scale for Geriatric patients; nr=not reported; PE=physical exercises; RoB=Risk of Bias.

Figure – Flow diagram of systematic reviews selection process