



Meta-analyses

Association between phase angle from bioelectrical impedance analysis and level of physical activity: Systematic review and meta-analysis



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SUMMARY

Objective: To evaluate the relationship between physical activity and phase angle.

Design: Systematic Review and Meta-analysis.

Data sources: Electronic searches of MEDLINE (via PUBMED), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), SciELO, LILACS, SPORTDiscus, Scopus, and Web of Science from inception to December 10th, 2017.

Eligibility criteria for selecting studies: The PICOS strategy was defined, in which “P” corresponded to participants of any age, sex or ethnicity, “I” indicated any type of physical activity program, “C” denoted lack of exercise or irregular physical activity, “O” corresponded to the phase angle obtained by bioimpedance, and “S” indicated longitudinal or cross-sectional studies.

Results: In cross-sectional studies the phase angle was higher among the active individuals (MD = 0.70; 95% CI: 0.48, 0.92, $P < 0.001$), with low heterogeneity ($I^2 = 0\%$; $P = 0.619$). In longitudinal studies, the mean of the difference of phase angles from the baseline was significantly higher for the active group than the control group (MD = 0.30; 95% CI: 0.11, 0.49, $P = 0.001$), with low heterogeneity ($I^2 = 13\%$, $P = 0.331$). No evidence of publication bias was found and the overall risk of bias was moderate to high.

Summary/conclusion: The positive association of physical activity with phase angle reinforces the importance of routinely including exercise in health care. We also identified the need for further studies to define with different types, intensities and frequencies of exercises should be conducted in order to find the best dose-effect relationship.

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1. Introduction

Phase angle (PhA) is considered to be an important parameter, which is calculated directly from the primary values of the resistance and reactance of the bio-impedance, in clinical use, as it appears to reflect cellular health, body cell mass, and the integrity of

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Summary box**What is already known**

- Phase Angle reflects cellular health and integrity of the cell wall and it has been postulated as a prognostic factor in critically ill patients
- Adequate level of physical activity is key to prevent and treat chronic diseases

What are the new findings

- Physical activity has a positive association with phase angle.

the cell wall [1]. Further, ill patients appear to have lower PhA values than healthy individuals, which may predict worse health outcomes [2,3] and mortality [4]. Therefore, PhA has been proposed as a prognostic factor for the diagnosis and monitoring of various diseases [5–8]. For instance, lower PhA appears to be a prognostic factor predicting mortality in patients with liver cirrhosis [2], undergoing hemodialysis [9–11], with chronic obstructive pulmonary disease [12], or with cancer [13–15]. It is also associated with malnutrition [16–18].

It is widely acknowledged that physical exercise has positive effects on the prognosis of all the conditions previously mentioned [19–21]. Maintenance of an adequate level of physical activity (PA) is essential in the prevention and treatment of chronic diseases [21]. In addition, engaging in exercise programs improves the prognosis of cancers, chronic kidney diseases, and heart conditions [20,22–24]. Evidence suggests that active people, even those with chronic disease, have better PhA [25,26], and as a consequence, better health outcomes. However, research data on modifiable factors which may help maintain or increase PhA are scarce.

The aim of this study was to evaluate the association between physical activity and phase angle, and to conduct a meta-analysis of the findings. In order to increase the precision of the results, only studies with a control group, i.e. individuals allocated in a control group without exercise or subjects that do not reach the recommended levels of moderate to intense physical activity, were included.

2. Methods**2.1. Protocol and registration**

This systematic review and meta-analysis were performed in accordance with the PRISMA guidelines [27]. The systematic review protocol was registered with the PROSPERO database: (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=20214).

2.2. Eligibility criteria

This systematic review and meta-analysis were conducted in order to answer the question: Is physical activity associated with a higher phase angle? The PICOS strategy was defined, in which “P” corresponded to participants of any age, sex or ethnicity, “I” indicated any type of physical activity program, “C” denoted lack of exercise or irregular physical activity, “O” corresponded to the

phase angle obtained by bio-impedance, and “S” indicated longitudinal or cross-sectional studies.

2.3. Exclusion criteria

The following exclusion criteria were used: (A) duplicated publications or studies additional to those already included; (B) studies which did not evaluate the association between PA and PhA; (C) case studies, case series, experimental models, reviews, responses, and editorials; (D) studies without control group; and (E) studies reporting correlation between physical activity and phase angle without classifying the subjects into active and inactive.

2.4. Sources of information and search strategy

We used the following sources to identify relevant studies from inception to December 10th, 2017: MEDLINE (via PUBMED), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), SciELO, LILACS, SPORTDiscus, Scopus, and Web of Science. We tried to identify additional studies by scanning through the reference lists of relevant publications and reviews. Studies published in any language were included in the analysis.

The detailed search strategy can be found online as supplementary material: http://www.crd.york.ac.uk/PROSPEROFILES/20214_STRATEGY_20151118.pdf.

2.5. Study Selection

To select the studies to be assessed further, two reviewers (EM and MA) independently scanned the titles and abstracts of each identified study. The full texts of all potentially relevant articles were accessed and investigated. A third reviewer (RM) reviewed any differences in opinion, to make a final decision.

2.6. Data extraction

Data from the selected studies were extracted independently by two reviewers (EM and MA), using data extraction forms created by the authors for this review. The following data were extracted: name of the first author, year of publication, study location, population, type of study, type of exercise assessment (objective or subjective), main results, and sample size.

2.7. Type of exercise assessment

Physical Activity has four dimensions (Mode or Type, Frequency, Duration, and Intensity) and four domains (Occupational, Domestic, Transportation, and Leisure). These dimensions and domains can be objectively verified with wearable technology and monitoring the vital signs. Physical activity can also be assessed in a subjective manner using validated reminders and questionnaires. The choice of the objective or subjective method of PA verification depends on the level of precision required, on the dimensions and domains to be checked, and on the value available for the investment [28].

2.8. Risk of bias in individual studies

To analyze the risk of bias in clinical trials, we used the Cochrane Collaboration's tool [29]. We analyzed the degree of randomization, allocation concealment, blinding of participants, selection bias, blinding the researchers analyzing the outcomes, and report of the selective outcome.

In observational studies, we used an evaluation tool for assessment of cohort and cross-sectional studies recommended by the

National Institute of Health, U.S. Department of Health and Human Services [30].

2.9. Summary measures and data synthesis

A meta-analysis was conducted separately for cross-sectional and longitudinal study designs (clinical trials and longitudinal studies). Mean of differences in the effective size measure was used to estimate the association between physical activity and phase angle. Mean of differences in the phase angle values was used for cross-sectional studies, while the mean difference of deltas (change from baseline) was used for longitudinal studies. In case of studies where the standard deviations of deltas were missing, imputation was performed using a conservative approach (using correlation equal to zero). The Cochran Q test and the I^2 statistics were used to assess heterogeneity among studies. Random-effects models on two separate sub-groups were designed in order to explore the expected heterogeneity among studies. The first sub-group was made according to health status (subjects with chronic conditions or healthy subjects), and the second according to the method used to verify PA levels of individuals (objective or subjective measurement). The sensitivity was analyzed based on whether exclusion of one study at a time significantly modified the heterogeneity or the results, and by considering study design in longitudinal studies (observational follow-up, randomized clinical trial, or non-randomized clinical trial). A funnel plot was generated to investigate the possibility of publication bias. All the analyses were performed using the statistical software 'R' version 3.4.0.

3. Results

The initial search returned 13,546 studies, of which 8,898 were duplicate. We screened the remaining 4,648 titles and abstracts, of which 4,628 articles were excluded: 4,170 because they did not evaluate the association between PA and PhA, and 458 because they were case studies, cases series, experimental models, reviews, responses, and editorials. Twenty articles were selected for full-text reading, of which 11 were excluded: six due to the lack of a control group and five because they only reported a correlation between physical activity and phase angle. Thus, nine articles were ultimately included in our systematic review and meta-analyses (Fig. 1).

The general characteristics of the selected studies are summarized in Table 1. Taken together, the studies reported data from 575 subjects. Five studies were longitudinal: four clinical trials and one follow-up [26,31–34], and four studies were cross-sectional [25,35–37]. Among the clinical trial studies, three were Randomized Clinical Trials (RCT) [31–33] and two were Non-Randomized Clinical Trials [26,34]. The clinical trial study by Zanelli et al. was designed to evaluate the effect of creatine supplementation on resistance training practitioners. We used the baseline data for each group for our meta-analysis. The majority of the studies were conducted in different European countries [25,26,35–37]. The authors used different devices to perform the bioimpedance test (Table S2).

The participants (age, athletic condition, and health condition), type of exposure (resistance training, aerobic training, or

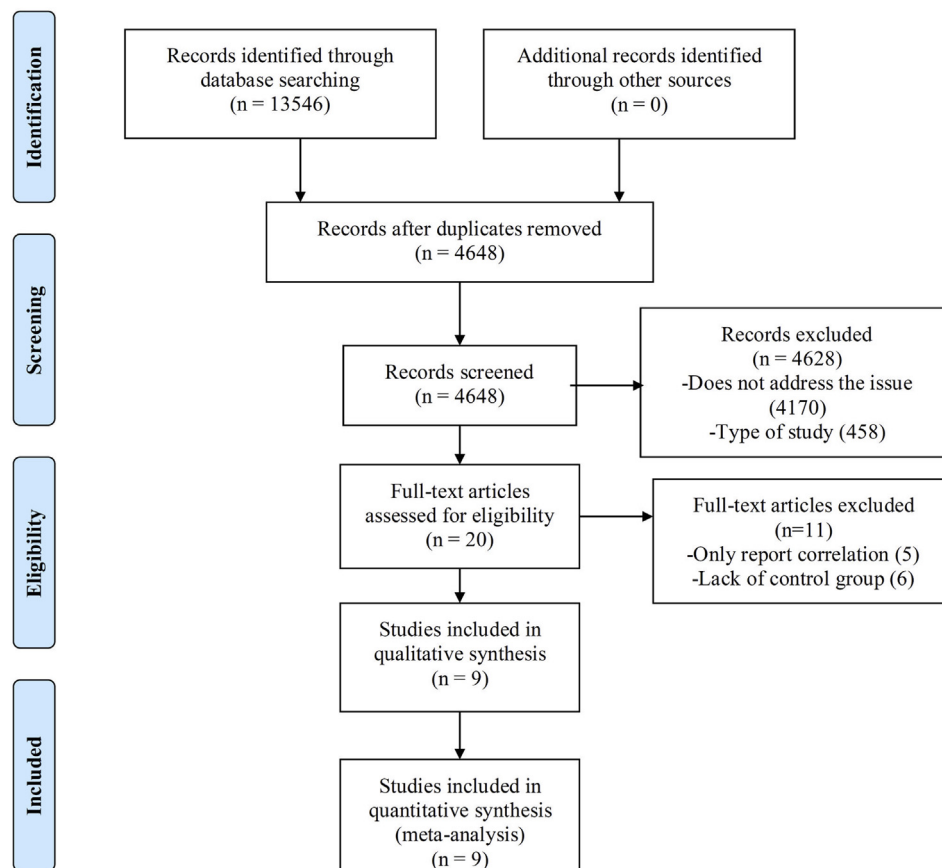


Fig. 1. Flow diagram of study selection.

Table 1
General characteristics of the selected articles.

Author, Year	Design	N	Age (years)	Health condition	Exercise Type	Physical activity assessment	Country
Ribeiro A S, 2017 [31]	Randomized Clinical Trial	50	≥60	Healthy	Resistance training	Subjective	Brazil
Souza M F, 2016 [32]	Randomized Clinical Trial	41	67.2 ± 4.5	Healthy	Resistance training	Subjective	Brazil
Martin-Alemañy G, 2016 [33]	Randomized Clinical Trial	36	34 (24.5–43)	Dialysis Patients	Resistance training	Subjective	Mexico
Zanelli J C S, 2015 [34] ^a	Clinical Trial	14	22.6 ± 1.45	Healthy	Resistance training	Objective	Brazil
Jungblut SA, 2009 [26]	Clinical Trial	42	Exercise = 68 Control = 72	COPD	Concurrent training	Subjective	Germany
Meleleo, D, 2017 [37]	Follow-up	219	8–11	Healthy	Swimming gymnastics	Subjective	Italy
Jaramillo G C, 2013 [35]	Cross-sectional	78	63 ± 12	Dialysis Patients	Walk or Run	Objective	Spain
Cupsiti A, 2010 [25]	Cross-sectional	50	Exercise = 53.6 ± 11.6 Control = 63.3 ± 12.5	Dialysis Patients	Any	Objective	Italy
Marra M, 2009 [36]	Cross-sectional	45	Exercise = 18.9 ± 1.7 Control = 19.4 ± 2.4	Anorexia nervosa	Ballet	Subjective	Italy

Legend: N = Number of Subjects; COPD = Chronic Obstructive Pulmonary Disease.

^a Clinical trial designed to verify the effects of creatine supplementation on resistance training practitioners; beginners and experienced. For our meta-analysis we used the baseline data for each group.

concurrent training), and methods for assessment of physical activity (subjective and objective) were observed to be heterogenous.

Four studies were conducted on subjects with chronic conditions [25,26,33,35], three on patients undergoing dialysis [25,33,35] and one on patients with chronic obstructive pulmonary disease (COPD) [26]. Among the studies performed on healthy populations, two were conducted on older women [31,32], one on women with anorexia [36], one on resistance training practitioners [34], and one on athletic children [37]. The subjects received different types of training (intervention or exposure). Resistance Training (RT) was more frequently described, with four studies [31–34]. The other types of training described were Aerobic Training (AT) [35], concurrent training [26], swimming and gymnastics [37], ballet dancing [36], and any form of physical activity [25]. As for the tools used to assess PA in the five observational studies, two studies used objective measurements: one used accelerometers [25], and one used pedometers [35], while two used subjective tools [36,37]. Regarding the interventions performed in the five clinical trials, the three RCT used resistance training [31–33], one clinical trial used resistance training [34], and one used concurrent training [26].

3.1. Meta-analysis

In the cross-sectional studies, the active subjects presented a higher mean phase angle than controls (MD = 0.70; 95% CI: 0.48, 0.92, $P < 0.001$, Fig. 2), with low heterogeneity ($I^2 = 0\%$; $P = 0.619$). It was also observed that the differences between health status and method for assessment of physical activity were not significant ($P = 0.332$; $P < 0.253$, Fig. 2). The longitudinal studies (clinical trials or follow-up) indicated that the mean differences of the phase angles from baseline were significantly higher for the active group, when compared with the control group (MD = 0.37; 95% CI: 0.13, 0.61, $P = 0.002$, Fig. 2), with low heterogeneity ($I^2 = 13\%$, $P = 0.331$).

The differences between health status were not significant ($P = 0.7821$, Fig. 2). All studies had subjective measures of the level of exercise. There were no significant differences between clinical trials and follow-up studies ($P = 0.502$, Fig. 2). A sensitivity analysis was conducted after excluding one study by Martin-Alemañy et al., which had a high disparity in results [33] (Supplementary Fig. S1). Although this did not change the overall direction of the effect (MD = 0.39; 95% CI: 0.19, 0.58, $P < 0.001$), heterogeneity was observed to decrease ($I^2 = 0\%$). In a more detailed sensitivity analysis in which one study was excluded at a time, the mean difference in both cross-sectional and longitudinal studies did not change with the exclusion of any of the studies. Analysis of the Funnel Plot did not show a tendency for publication bias, both

among cross-sectional and longitudinal studies (Supplementary Figs. S2 and S3).

3.2. Risk of bias

The risk of overall bias was moderate to high. Among the clinical trials, we observed that two studies were at risk of bias in terms of randomization and allocation (Selection Bias). Given the nature of an exercise intervention, it is not possible to blind participants, but the authors of three papers did not declare the blinding with respect to the analysis of the outcome (detection bias). None of the clinical trials were at risk of bias in relation to incomplete outcome data (attrition bias) or selective reporting (reporting bias) (Supplementary Fig. S4).

Only one of the observational studies had an overall good rating in terms of quality, while two were rated as fair and one as poor (Supplementary Table 1).

4. Discussion

Our systematic review found evidence that physical activity had a positive effect on phase angle. These results were corroborated by the meta-analysis of data from clinical trials, showing evidence of a causal relationship, wherein differences in PhA from the baseline were significantly higher for the active group than the control group. The magnitude of the increase in phase angle was not statistically different between healthy individuals or those with chronic disease, either by type of study or by type of physical activity evaluation, which shows great consistency of results.

Different mechanisms appear to be involved in the process by which PA causes improvement in PhA values, resulting in better integrity and functionality of the cell membrane, changes in intracellular composition, and enhanced tissue capacity [1,38]. Although exercise initially appears to negatively affect the cell membrane [39], this is followed by a super compensation in which the acute harmful effect of exercise on the individual is compensated by an improvement of the structure [40], i.e. comply with the principle of the general adaptation syndrome [41].

The phase angle is inversely proportional to resistance; resistance, in turn, depends on both intra and extracellular water [42]. Physical training, especially when it causes an increase in muscle mass, can lead to increase the intracellular water [43], which reduces the resistance and consequently leads to an increase of the phase angle. The reactance is directly proportional to the phase angle and depends on the integrity of the cell membrane [42]. Well-conducted exercise may be a factor in enhancing the integrity of

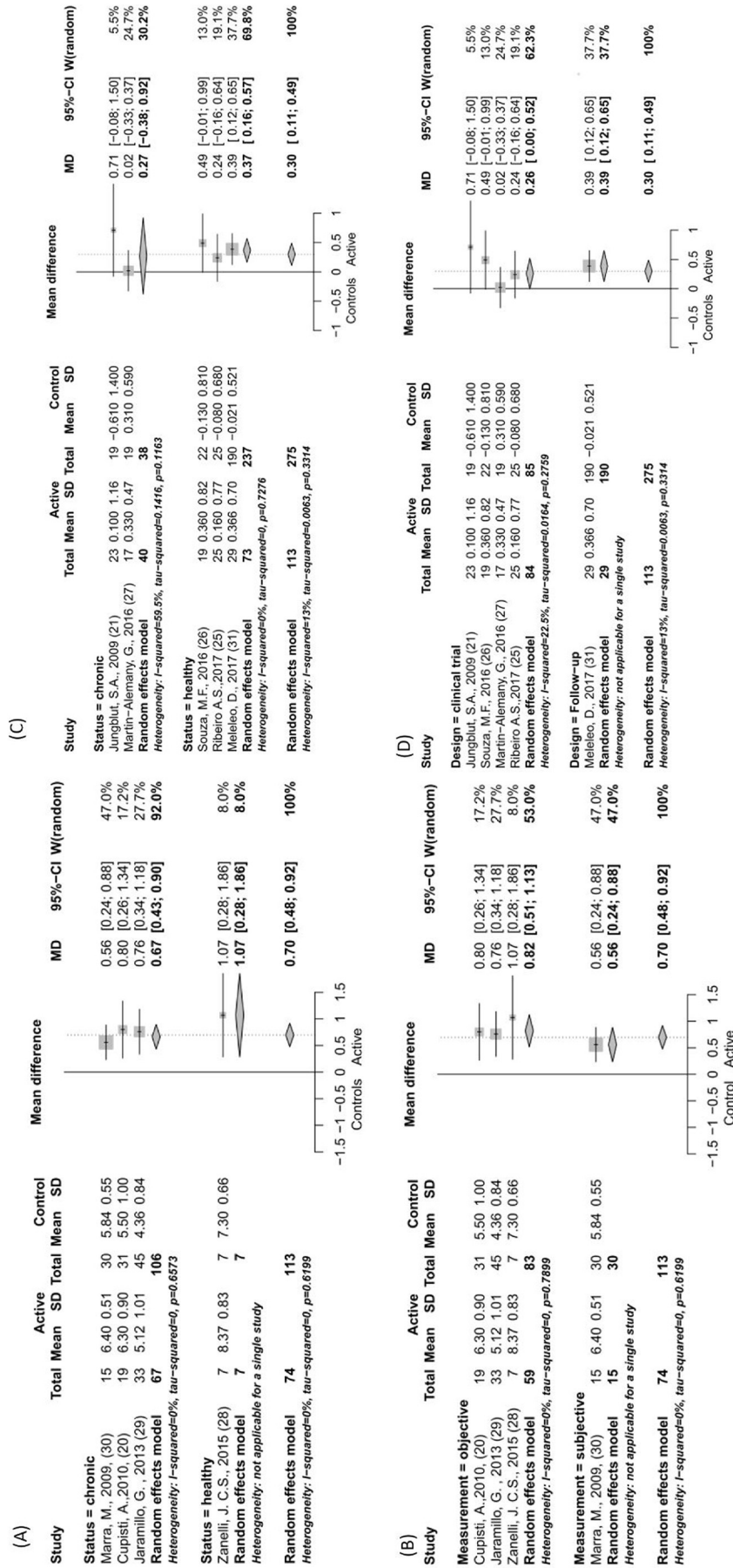


Fig. 2. Meta-analyses.

this membrane by the mechanism of overcompensation described above [41]. Another factor that increases the reactance is the total cellular mass [44]. Training can lead to the increase of the total cellular mass [45], which leads to the increase of the reactance and the consequent increase of the phase angle. Measurement of the phase angle can, therefore, be an indicator of the effects of physical exercise on the health of the cell and, consequently, on the health of the individual. There are also authors who argue that the phase angle can be used, in clinical practice, as an indicator of the level of physical activity of the individual [46].

The type of exercise most studied among the included articles was resistance training. This type of training appears, alone or in conjunction with other training modalities, in five of the nine articles. In addition, this training modality appears in all clinical trials. Resistance training was the only type of exercise in which we found a study that attempted to identify the effect of changes in the volume intensity ratio. This study [31] identified that this training modality, when performed in elderly women with different methods has positive effects on the phase angle. However, there are other methods and different relationships between volume, intensity and frequency in training against resistance, and especially in other types of exercise that must be tested to find the best dose-benefit relationship in relation to phase angle. Furthermore, we did not find studies investigating whether the combination of more than one type of exercise, the concurrent training, is superior to the isolated training. Therefore, the present study supports the hypothesis that exercise is positively associated with phase angle and therefore leads to enhanced cell membrane integrity and improved cell health. However, the relationships between domains and dimensions and, especially, the best dose-benefit relationship are open questions.

Although the studies included different populations, types of interventions, did not specify the recommended criteria for performing bioimpedance, items that affect the results, the heterogeneity of the analyzes was low and the direction of the effect went to the same side. The only study that the direction differed a little from the others was that of Martín-Alemañy [33], the exclusion of this study increases the effect of the results. These findings reinforce that in spite of all possible differences that could affect the results, the effect of the exercise continued to indicate the importance of this and suggests that in studies that are more homogeneous and in ideal scenarios to perform bioimpedance, this effect may be even greater.

Evidence demonstrates that larger PhA values are associated with lower risk of hospitalization, mortality, and cardiovascular events [4,47] in patients with chronic conditions [11,13–15,48]. This substantiates the importance of including PA routines with the aim of improving outcomes in patients with chronic diseases. In our systematic review, all four studies in patients with chronic conditions [25,26,33,35] reported a significant positive association between PhA and the level of PA. As the phase angle has been postulated as an indicator of cellular health, cell membrane integrity [49] and total cell mass [1], these results indicate that, even in patients with chronic diseases, exercise improves these indicators.

The quality of the studies in general was reasonable, but some items were poorly reported, especially among clinical trials. An unreported item was the procedure to blind the study. The participant in a study with exercise will always know if he is in the control group or not. However, the personnel that analyzes the phase angle can be blinded, which has not happened in some studies. Another source of risk of bias is absence of randomization in some studies, which may generate a selection bias, since individuals with a lower phase angle could be placed in the exercise group, which would predispose this group to greater increases in this variable due to the phenomenon of return to the mean [50].

However, when analyzing the effect size between the studies, there was no clinically significant difference between the studies with better or worse quality, which shows that this was not a determining factor for the observed results.

4.1. Strengths and limitations of the systematic review

The major strength of our systematic review is the inclusion of all available studies, by searching the “gray” literature as well as all major databases. We also did not limit the search by publication period or by language, furthermore we do not set limits in terms of age, type of diet and type or level of exercise performed. One of the problems that this could cause would be a great statistical heterogeneity among the studies, which was not verified in the meta-analyses.

A limitation of our study is the low methodological quality of the studies, as shown in the analysis of risk of bias. This limitation seems to be of little importance, as there is a great consistency in the results between the studies with reference to the positive effect of PA on the PhA.

5. Conclusions and future directions

Our study found that physical activity has a positive effect on phase angle, which is a prognostic marker of cell health. That is one more reason to support the inclusion of physical activity counseling in the clinical routine, treatment, and prevention of various chronic diseases. Also, our results suggest that the clinicians may include phase angle in the assessment of physical performance, since its evaluation, assessed by the BIA method is reliable, easy to measure, and repeatable.

These results are important for clinical, research, and routine scenarios, aiming for the better health and well-being of both healthy individuals and subjects with chronic diseases. Still, additional studies comparing different types, intensities, and frequencies of exercises should be conducted in order to find the best dose-effect relationship.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnu.2018.08.031>.

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