

# Reduced functional capacity in patients with Chagas disease: a systematic review with meta-analysis

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## Abstract

Reduced peak oxygen uptake ( $VO_2$ peak) is a common clinical finding in progressive Chagas disease. However, the disease stage in which functional impairment is detectable remains uncertain. The present study compared functional capacity between healthy controls and patients with different clinical forms of Chagas disease. A systematic review and meta-analysis (PROSPERO database CRD42017058353) was conducted following a search of the MEDLINE, Web of Science, CINAHL, and LILACS databases from September to December 2017 for articles published in English, Spanish, or Portuguese, with no date restrictions. We included studies that compared the  $VO_2$ peak between healthy and Chagas disease patients, stratified according to 3 clinical forms [no apparent cardiac disease, non-dilated Chagas heart disease (CHD), and dilated CHD]. Seven cross-sectional studies were included. Chagas disease patients without apparent cardiac disease (n=208) had  $VO_2$ peak values [mean difference, -1.55ml/kg/min; 95% confidence interval (CI), -4.98ml/kg/min to 1.88ml/kg/min] similar to those of healthy controls (n=105; p=0.38,  $I^2=52\%$ ). In non-dilated CHD (n=159),  $VO_2$ peak was 8.71ml/kg/min lower (95% CI, -13.99 to -3.42ml/kg/min) than in healthy controls (n=59; p=0.001,  $I^2=75\%$ ).  $VO_2$ peak was also significantly lower (mean difference, -9.30ml/kg/min; 95% CI, -11.34 to -7.25ml/kg/min) in dilated CHD patients (n=131) than in healthy controls (n=53; p<0.001,  $I^2=0\%$ ). Exercise capacity in Chagas disease patients without apparent cardiac disease is similar to that in healthy controls. Functional impairment in Chagas disease is detectable in the early stages of cardiac involvement, even in the absence of systolic dysfunction and signs of heart failure.

**Keywords:** Chagas disease. Functional capacity. Exercise testing. Systematic review.

## INTRODUCTION

Chagas disease remains a serious public health problem in Latin American countries. Approximately 6-7 million people worldwide are estimated to be infected with *Trypanosoma cruzi*<sup>1</sup>, which is endemic in 21 countries<sup>1</sup>, and 80% of the patients do not have access to diagnosis or appropriate treatment<sup>2</sup>, emphasizing the lack of attention to this disease<sup>3</sup>.

Recently, the Benznidazole Evaluation for Interrupting Trypanosomiasis trial (BENEFIT)<sup>4</sup> showed that parasitocidal treatment does not seem to reduce cardiac damage in Chagas heart disease (CHD), the most severe clinical form of the infection<sup>5</sup>. In contrast, exercise training has shown positive

effects on the overall patient health<sup>6</sup>. The benefits include a significant increase in functional capacity<sup>7-9</sup>, respiratory muscle strength<sup>9</sup>, quality of life<sup>7</sup>, and left ventricular ejection fraction (LVEF)<sup>9</sup>.

Nevertheless, the stage of disease in which reduced functional capacity can be observed remains unclear. Mady et al.<sup>10</sup> reported significant reduction in peak oxygen uptake ( $VO_2$ peak), even in the absence of signs and symptoms of heart failure. In contrast, other studies<sup>11,12</sup> reported that reduced functional capacity can be detected only in the advanced stage of the disease, with fatigue and dyspnea during ordinary physical activity as a well-defined marker of poor prognosis<sup>13,14</sup>.

As the stage of disease in which reduced functional capacity can be observed may be important in the adoption of cardiac rehabilitation therapies, the present study compared functional capacity between healthy individuals and patients with different clinical forms of Chagas disease.

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## METHODS

### Study design

This systematic review aimed to determine the clinical form of Chagas disease in which reduced functional capacity is detectable. The study was registered in the PROSPERO database CRD42017058353 and edited following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>15</sup>.

### Search strategy and study selection

Potential studies were identified through a systematic search. The databases used were MEDLINE, Web of Science, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Latin American & Caribbean Health Sciences Literature (LILACS) for relevant studies, without date restrictions from inception until December 2017. The search was conducted independently by 2 authors (HSC and MMOL) from September to December 2017. Disagreements were resolved by a third reviewer (PHSF). Search terms included words related to Chagas heart disease, Chagas cardiomyopathy and functional capacity. The following strategy was used for the PubMed search—["Chagas Disease"(Mesh) OR "Chagas heart disease" OR "Chagas Cardiomyopathy"(Mesh)] AND ["Exercise"(Mesh) OR "Exercise Test"(Mesh) OR "functional capacity" OR "oxygen consumption"(Mesh) OR "oxygen uptake" OR "VO<sub>2</sub>peak"]—and was modified for each database.

### Eligibility criteria

Eligibility criteria included studies a) that evaluated patients diagnosed with Chagas disease and defined the criteria; b) that assessed the VO<sub>2</sub>peak expressed in ml/kg/min; c) with at least 1 group of patients with Chagas disease and 1 control group; d) written in English, Spanish, or Portuguese.

Those with positive serology for *T. cruzi* but without signs, symptoms, or evidence of changes on the electrocardiogram or chest radiogram were considered patients with Chagas disease without apparent cardiac disease. Non-dilated CHD patients were defined according to the presence of arrhythmias and intraventricular and atrioventricular conduction disorders with normal ventricular function<sup>16</sup>. Patients with ventricular dysfunction (LVEF<50%) and cardiac dilation on echocardiography were considered to have dilated CHD.

Exclusion criteria were review studies, articles in duplicate, animal studies, and those that did not match the objective of this review. There were no restrictions on the year of publication until December 2017. Studies of authors using the same population were excluded, as well as those without adequate statistical analysis.

### Quality assessment

The quality assessment was evaluated using the adapted form of the Newcastle Ottawa cohort scale for cross-sectional studies<sup>17</sup>. The scale consists of 8 items grouped under 3 topics, namely, *selection, comparability and confounders*, and *outcome*.

## Outcomes and data analysis

The following data were extracted from the included articles: author, publication year, characteristics of the sample, and VO<sub>2</sub>peak value and method of measurement.

Chagas disease patients were stratified according to the clinical form of the disease, that is, Chagas disease without apparent cardiac disease, patients with normal left ventricular dimensions and function (non-dilated CHD), and patients with a dilated left ventricle with impaired ventricular systolic function (dilated CHD).

The primary outcome measure was the difference in VO<sub>2</sub>peak, expressed in ml/kg/min, between healthy individuals and Chagas disease patients (Chagas disease without apparent cardiac disease, non-dilated CHD, and dilated CHD).

The software Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct meta-analyses for the outcome measures, reported as the mean difference with 95% confidence interval (CI). Heterogeneity was defined as low, moderate, or high according to I<sup>2</sup> values (25, 50, or 75%, respectively). A forest plot was used to display the results of the meta-analysis. Data analysis was performed using the fixed-effects model when the results showed low heterogeneity (I<sup>2</sup> ≤25%) and the random-effects model when the results showed moderate or high heterogeneity (I<sup>2</sup> >25%).

## RESULTS

### Flow of papers through the review

The electronic search strategy identified 363 studies but 147 (40.5%) were duplicates. After screening titles and abstracts, 187 (51.5%) papers were excluded. Twenty-five articles were review studies, 58 did not perform maximal exercise testing, 26 consisted of a sample without Chagas disease, 24 did not have a healthy control group, 40 conducted animal studies, and 14 articles were not found.

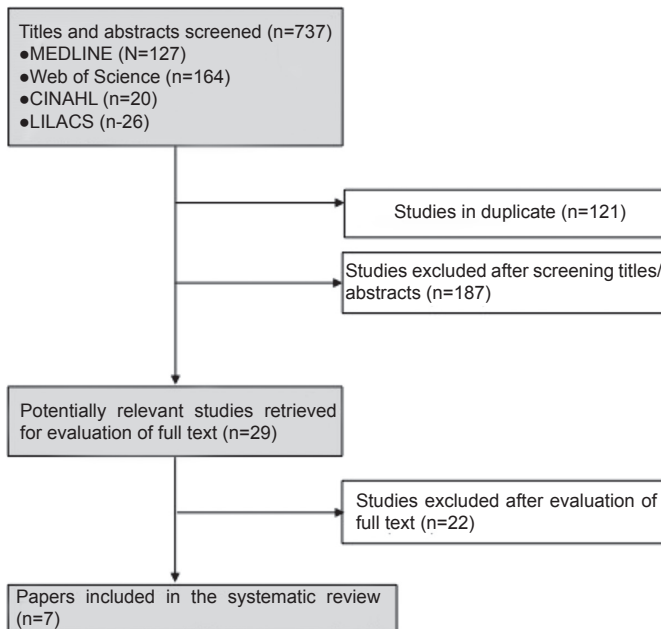
After reading the full text, 16 articles were excluded for failing to meet the objective of the present review, 1 did not define the clinical form of patients with Chagas disease, 1 did not report the sample size, and 3 were by authors who evaluated the same group of study patients in already included studies. Another article did not report VO<sub>2</sub>peak in ml/kg/min. A total of 7 articles were included in the present review. **Figure 1** outlines the flow of papers through the review.

### Participants

Four studies<sup>12,18-20</sup> compared the functional capacity of healthy individuals to patients with Chagas disease without apparent cardiac disease. Three studies<sup>12,20,21</sup> reported the difference in VO<sub>2</sub>peak between healthy individuals and patients with non-dilated CHD. Finally, 4 articles<sup>12,20,22,23</sup> demonstrated the difference in functional capacity between healthy subjects and patients with dilated CHD. Two studies<sup>12,20</sup> compared the VO<sub>2</sub>peak of healthy subjects with more than 1 group with Chagas disease.

### Outcomes

The treadmill was used to evaluate VO<sub>2</sub>peak in 6 studies<sup>18-23</sup> and the cycle ergometer was used in only 1 paper<sup>12</sup>. The VO<sub>2</sub>peak



**FIGURE 1:** Flow of studies through the review. **MEDLINE:** Medical Literature Analysis and Retrieval System Online; **CINAHL:** Cumulative Index to Nursing and Allied Health Literature; **LILACS:** Latin American & Caribbean Health Sciences Literature.

was directly assessed using gas analysis in 3 articles<sup>12,21,23</sup> and estimated by formulas in 4 studies<sup>18-20,22</sup>.

**Quality of papers**

The mean Newcastle Ottawa scale score adapted for cross-sectional studies was 7.3 points (range from 6.0 to 9.0). All studies adequately verified the primary outcome and statistically demonstrated the difference between the groups. However, only 1 study reported the sample calculation. The scores according to the Newcastle Ottawa scale and the characteristics of the included studies are summarized in **Table 1**.

**VO<sub>2</sub> peak in patients with Chagas disease without apparent cardiac disease**

The mean score for quality was 7.0 points (ranging from 6.0 to 9.0). Only 1 (25%) study evaluated VO<sub>2</sub> peak directly using gas analysis. One paper used the cycle ergometer and 3 used the treadmill in exercise testing.

No study found significant differences in the VO<sub>2</sub> peak between healthy individuals and patients with Chagas disease without apparent cardiac disease. The forest plot (**Figure 2**) showed that patients with Chagas disease without apparent cardiac disease (n=208) had VO<sub>2</sub> peak values (mean difference

**TABLE 1:** Characteristics of included studies that compared the VO<sub>2</sub> peak between healthy individuals and Chagas disease patients.

Study	Sample characteristics	VO <sub>2</sub> peak (ml/kg/min)	VO <sub>2</sub> peak evaluation	p-value	Quality
<b>Comparison between healthy subjects and Chagas disease patients without apparent cardiac disease</b>					
Costa et al. (2015)	Healthy Control=38 (42% females, 44±9.1 years, LVEF 69.7±5.2%) ChD without cardiac disease=75 (52% females, 44.7±8.7 years, LVEF 68.2±5.6%)	40.4±7.6 40.6±10	Treadmill Estimated VO <sub>2</sub>	No difference	9
De Oliveira, Pedrosa, Gianella-Neto (2000)	Healthy Control=15 (All males, 36±9 years) ChD without cardiac disease=17 (All males, 47±11 years, LVEF 68±4%)	31±12 24±5	Bicycle Direct VO <sub>2</sub>	No difference	6
Rabelo et al. (2013)	Healthy Control=28 (57% females, 52±8 years, LVEF 63±3%) ChD without cardiac disease=64 (63% females, 50±12 years, LVEF 65±5%)	26±11 28±11	Treadmill Estimated VO <sub>2</sub>	No difference	6
Rocha et al. (2006)	Healthy Control=24 (29% females, 35.6±9.3 years, LVEF 64% [61-66]) ChD without cardiac disease=52 (40% females, 39.8±9 years, LVEF 62% [60-65])	49.4±10.1 45.8±10.6	Treadmill Estimated VO <sub>2</sub>	No difference	7
<b>Comparison between healthy subjects and non-dilated Chagas heart disease patients</b>					
De Oliveira, Pedrosa, Gianella-Neto (2000)	Healthy Control=15 (36±9 years) Non-dilated CHD=23 (49.6±11 years)	31±12 23.6±8.1	Bicycle Direct VO <sub>2</sub>	No difference	6
Mady et al. (1997)	Healthy Control=20 (All males, 32.9±6.1 years) Non-dilated CHD=18 (All males, 29.2±5.6 years)	36.98±5.45 24.32±4.25	Treadmill Direct VO <sub>2</sub>	<b>&lt;0.001</b>	8
Rocha et al. (2006)	Healthy Control=24 (29% females, 35.6±9.3 years, LVEF 64% [61-66]) Non-dilated CHD=118 (44% females, 41.8±9.2 years, LVEF 60% [50-64])	49.4±10.1 44.2±8.6	Treadmill Estimated VO <sub>2</sub>	<b>&lt;0.05</b>	7
<b>Comparison between healthy subjects and dilated Chagas heart disease patients</b>					
Baiao et al. (2013)	Healthy Control=15 (47% females, 47.3±9.1 years) Dilated CHD=15 (47% females, 50.3±5.7 years, mean LVEF 36%)	38.53±7.81 28.46±6.58	Treadmill Estimated VO <sub>2</sub>	<b>0.004</b>	6
De Oliveira, Pedrosa, Gianella-Neto (2000)	Healthy Control=15 (36±9 years) Dilated CHD=12 (55±9 years, LVEF 28±8%)	31±12 19±5	Bicycle Direct VO <sub>2</sub>	<b>&lt;0.05</b>	6
Mady et al. (1996)	Healthy Control=23 (All males, 35±8.7 years, LVEF 75.1±3.2%) Dilated CHD=104 (All males, 24.5±2.9 years, LVEF 42±11.7%)	33.3±5.6 24.5±2.9	Treadmill Direct VO <sub>2</sub>	<b>&lt;0.001</b>	9

**VO<sub>2</sub> peak:** peak oxygen uptake; **ChD:** Chagas disease; **CHD:** Chagas heart disease; **LVEF:** left ventricular ejection fraction. Values highlighted in bold were statistically significant (p<0.05).

-1.55ml/kg/min; 95% CI from -4.98ml/kg/min to 1.88ml/kg/min) similar to those of healthy subjects (n=105) (p=0.38). The heterogeneity of the comparison was moderate (I<sup>2</sup> = 52%).

### VO<sub>2</sub>peak in non-dilated CHD patients

The mean score for quality was 7.0 points (ranging from 6.0 to 8.0). Two (66.6%) studies evaluated VO<sub>2</sub>peak directly using gas analysis. One paper used the cycle ergometer and the other 2 performed exercise testing with a treadmill.

Of the 3 studies included, only 1 (33.3%) reported no significant difference in VO<sub>2</sub>peak between healthy subjects and dilated CHD patients and 2 (66.6%) showed that the VO<sub>2</sub>peak was significantly lower in non-dilated CHD patients than in healthy subjects.

The forest plot (Figure 3) showed that VO<sub>2</sub>peak was 8.71ml/kg/min lower (95% CI -13.99 to -3.42ml/kg/min) in non-dilated CHD patients (n=159) than in healthy subjects (n=59) (p=0.001). The heterogeneity of the comparison was high (I<sup>2</sup> = 75%).

### VO<sub>2</sub>peak in dilated CHD patients

The mean score for quality was 7.0 points (ranging from 6.0 to 9.0). Two (33.3%) studies evaluated VO<sub>2</sub>peak directly using gas analysis. One (33.3%) paper used the cycle ergometer and 2 (66.6%) performed maximum exercise testing with a treadmill.

All 3 included studies showed that the VO<sub>2</sub>peak was significantly lower in dilated CHD patients than in healthy subjects. The forest plot (Figure 4) showed that VO<sub>2</sub>peak was significantly lower (mean difference 9.30ml/kg/min; 95% CI -11.34 to -7.25ml/kg/min) in dilated CHD patients (n=131) than in healthy subjects (n=53) (p<0.001). The analysis was homogeneous (I<sup>2</sup> = 0%).

## DISCUSSION

The VO<sub>2</sub>peak has been widely used in assessing the functional capacity of patients with Chagas disease and is

considered a potential prognostic marker<sup>24</sup>. However, the association between functional impairment and the stage of disease in which it is detectable has been unclear. To our knowledge, this is the first study to systematically determine the stage of Chagas disease at which reduced exercise capacity can be observed. The main findings of the present study were: 1) patients with Chagas disease without apparent cardiac disease have VO<sub>2</sub>peak values similar to those of healthy individuals and 2) patients with CHD, even with preserved systolic function, showed a significant reduction in functional capacity when compared to healthy individuals.

For patients with Chagas disease without apparent cardiac disease, no study included in this review reported reduced functional capacity in this group of patients compared to that in the healthy subjects. In fact, patients with Chagas disease without apparent cardiac disease have excellent prognosis, similar to that of healthy individuals. However, although VO<sub>2</sub>peak values are within the normal range, exercise tests in these patients are highly recommended since Chagas patients present a greater number of exercise-induced arrhythmias, both during exercise and the recovery phase<sup>18</sup>.

In patients with non-dilated CHD, 2 studies found a significant decrease in VO<sub>2</sub>peak compared to that in the healthy subjects, and 1 reported no difference between these groups. The forest plot showed a significant difference in functional capacity between the non-dilated CHD and healthy control groups. The initial phase of Chagas cardiac disease is usually characterized by impairment in electrical stimulus formation and conduction. As shown by electrocardiography, the changes in ventricular function are discrete and segmental, but may indicate subclinical heart disease capable of affecting the functional status. According to Mady et al.<sup>10</sup>, electrocardiographic changes present from the early stages of disease lead to significant myocardial damage that may reduce exercise capacity. However, we believe that these results should be interpreted with caution, since the meta-analysis showed high heterogeneity. Chagas disease is

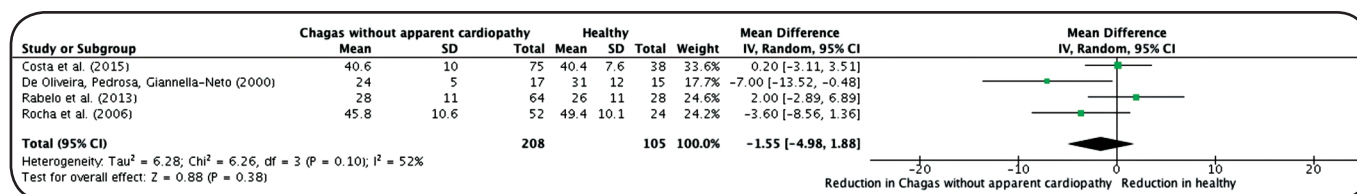


FIGURE 2: Mean difference in VO<sub>2</sub>peak between patients with Chagas disease without apparent cardiac disease and healthy controls. SD: standard deviation; 95% CI: 95% confidence interval; VO<sub>2</sub>peak: peak oxygen uptake.

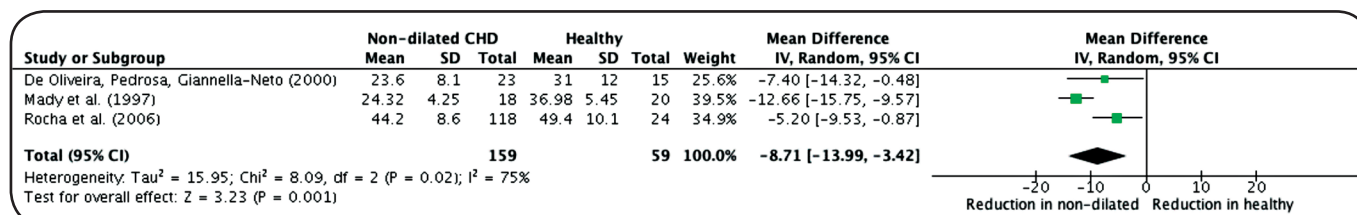
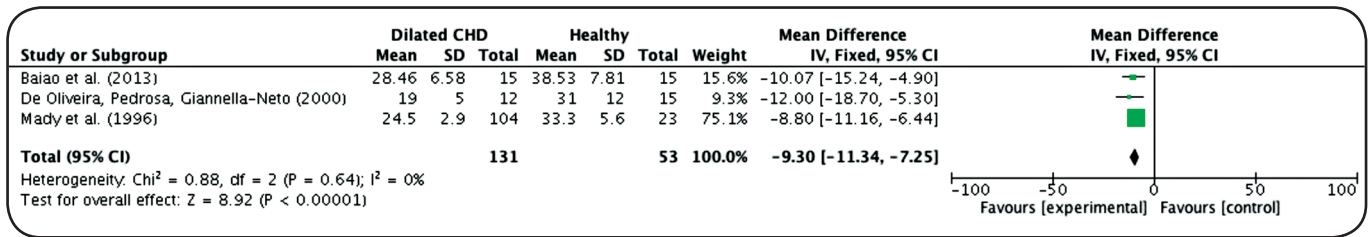


FIGURE 3: Mean difference in VO<sub>2</sub>peak between non-dilated CHD patients and healthy controls. CHD: Chagas heart disease; SD: standard deviation; 95% CI: 95% confidence interval; VO<sub>2</sub>peak: peak oxygen uptake.





**FIGURE 4:** Mean difference in  $VO_{2peak}$  between dilated CHD patients and healthy controls. **CHD:** Chagas heart disease; **SD:** standard deviation; **95% CI:** 95% confidence interval;  **$VO_{2peak}$ :** peak oxygen uptake.

characterized by great heterogeneity in clinical presentation. With regard to functional capacity, for example, the included studies showed a standard deviation of up to 12ml/kg/min. Furthermore, heterogeneity in the observational studies may be frequent and more common than in interventional studies<sup>25</sup>.

In the analysis of patients with dilated CHD, all studies showed significantly lower  $VO_{2peak}$  values compared to those in healthy subjects. The forest plot confirmed this result, with homogeneity among the studies. Briefly, patients with dilated CHD have  $VO_{2peak}$  values 9.30ml/kg/min lower than healthy patients, equivalent to almost 3 metabolic equivalents (METs). Some findings may suggest the functional impairment at this stage of the disease. The presence of symptoms of heart failure, such as fatigue and dyspnea, may be the most significant. These symptoms limit the patient's ability to exercise<sup>26</sup>, especially in association with abnormalities in the structure of skeletal muscle<sup>27</sup>. In addition, reduced cardiac output, one of the hallmarks of heart failure<sup>28</sup>, implies lower blood flow to the muscles used during exercise and early lactate accumulation. Respiratory muscle weakness may also reduce functional capacity, as previously reported in patients with heart failure<sup>29</sup>. Other factors, such as progressive deterioration of ventilatory response<sup>30</sup> and chronotropic incompetence<sup>20</sup>, can also account for functional impairment. Finally, it may also be possible that the fear of exercise and the discomfort caused by exercise-induced arrhythmias may lead to progressive physical inactivity.

This review had some strengths and limitations. The mean quality score of 7.3 for the included studies was good<sup>31</sup>. However, there was a major difference in the mean age among the groups. In addition, few studies were included in each meta-analysis. The heterogeneity among the studies included in the meta-analysis was high for the comparison between non-dilated CHD and healthy individuals. In addition, since there was no restriction on the date of publication, some studies could not be found, especially the oldest ones. Finally, publication bias inherent to systematic reviews was avoided by including studies published in languages other than English.

## CONCLUSION

Patients with Chagas disease without apparent cardiac disease have functional capacity similar to that of healthy individuals. In patients with the cardiac form of the disease, even in the absence of systolic dysfunction, functional capacity is markedly decreased, and exercise training should be mandatory in this population.

## Conflict of interest

All authors should disclose any type of conflict of interest during the development of the study.

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