MedicalExpress

REVIEW

A meta-analysis of cardiopulmonary exercise testing in pre-pubertal healthy children produces new information

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The objective of the paper was to analyze cardiopulmonary data and functional capacity in healthy children who have undergone ergospirometry. A systematic meta-analysis review of ergospirometry in children was performed based on reports indexed in PubMed, Bireme, and Embase. End points were age, sex, body mass index, maturation evaluation, the type of ergometer used for ergospirometry, and cardiopulmonary related values (peak heart rate and peak oxygen consumption [VO_2]). Twenty articles were selected, which included 3,808 children, averaging 9.1years of age. A treadmill was used in 55% of the trials, and a cycle ergometer in the other 45% studies included in this analysis. The following statistically significant results were found: on subgroup analysis, peak VO_2 values in boys on the treadmill was 20% higher than peak VO_2 values in girls on the cycle ergometer; peak VO_2 values in boys on the treadmill were 18% greater than that for girls on the same ergometer. BMI was inversely correlated with peak VO_2 in the total analysis, and in female subjects on cycle ergometers. Peak heart rate during the ergospirometrical test was 5.6 BPM higher than the estimated 95% maximum heart rate. Most of the ergospirometrical parameters had not been reported in the original trials analyzed here. We conclude that peak VO_2 value for pre-pubertal children are circa 18% higher in boys vs. girls and overall higher in treadmill vs. cycle ergometers.

KEYWORDS: Cardiopulmonary function, Cardiopulmonary exercise testing, Peak oxygen consumption.

Tavares AC, Bocchi EA, Teixeira-Neto IS, Guimarães GV. A meta-analysis of cardiopulmonary exercise testing in pre-pubertal healthy children produces new information. MedicalExpress (São Paulo, online). 2016;3(1):M160102

Received for Publication on October 11, 2015; **First review** on November 06, 2015; **Accepted for publication** on December 11, 2015; Online on January 04, 2016

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INTRODUCTION

Cardiopulmonary exercise testing (CPX) is frequently used to appraise healthy, athletic children,[1] but it is also performed to analyze several physiologic variables that influence respiratory, cardiac, and metabolic responses to progressive exercise and, therefore functional capacity.[2-4]

Peak oxygen consumption (peak VO_2), a CPX measurement, is one of the indicators of a person's cardiorespiratory condition. Peak VO_2 deficits are associated with increased chances of developing other risk factors for cardiovascular disease in adulthood[5,6] and also helps screening ill pediatric patients,[7-9] responses to treatment[10-14] and prognostic factors.[15]

Although pre-pubertal children are different from teens and adults, results from pediatric CPX have been published together with those of teens and adults. These combined values do not accurately reflect specific values for children.[16-17]

This lack of specific data for children emphasizes the need for separating data according to age groups for pattern analysis.[18] Knowing the CPX patterns of healthy children may be helpful for the development of clinical guidelines and better screening of ill pediatric populations in the future. Therefore, the aim of this study was to analyze cardiopulmonary data and functional capacity in healthy children who have undergone CPX.

METHODS

Literature search strategy

A systematic search of the PubMed, Bireme, and Embase databases was conducted to perform this meta-analysis, according to the recommendations of PRISMA.[19]

DOI: 10.5935/MedicalExpress.2016.01.02

The search was performed using the following keyword combinations: (1) child and VO_2, and (2) child and VO_2 peak. The results were limited to human studies published in English, Spanish, or Portuguese.

The selection was based first on the titles, second on the abstracts. Articles deemed relevant were retained for further analysis, which included a selection based on an analysis of the full text of the articles. The authors performed a double-check review of the list of possible trials.

Trials with cardiopulmonary test data in animals, child athletes, adolescents, or adults, and review articles were excluded. Trials that did not provide the number of patients included in the sample and the standard deviation value for the mean peak VO_2 found during the CPX were also excluded from final data collection. Papers with estimated peak VO_2 values by either formula or estimation, without complete data and without ergometer specification, were excluded as well.

Collected data

The following data were collected for final analysis from each study: a) number of children included; b) subjects' sex; c) subjects' age; d) subjects' height and weight; e) subjects' body mass index (BMI); if no BMI was provided, it was calculated as weight divided by height squared; f) whenever maturation was appraised, the respective scale was used in the evaluation as well; g) the ergometer used for cardiopulmonary testing (cycle ergometer or treadmill); and h) evaluation and cardiopulmonary related values (blood pressure, peak heart rate [HR], mean peak VO_2, and peak VO_2 standard deviation).

Peak VO_2 values were converted into mL/min/kg for comparisons. Thus, the confidence interval of the peak VO_2 values was calculated with $\mu \pm Z^*S/\sqrt{n}$, where μ is the reported mean value of the peak VO_2 in each trial; Z is the value related to the distribution reported in each trial; S is the reported standard deviation value of the peak VO_2 in each trial; and n is the number of subjects included in the sample.

Collected data included in the tables are expressed according to the type of ergometer used for the cardiopulmonary testing, cycle ergometer (C) or treadmill (T) and according to sex.

Manuscripts are cited sequentially and chronologically based on year of publication to better clarify data presentation and their analysis.

Statistical analysis

Data are expressed as collected from the original trials, as absolute numbers, with the exception of peak VO_2 values, for which confidence intervalswere calculated.

All the calculated results are expressed as mean ± standard deviation (SD). A Forest plot was used to elucidate the confidence intervals and mean values.

Statistical analyzes were performed with SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to check the normality of the population data. Parametric tests were used on the data with normal distribution.

The two-way ANOVA test was performed to determine the difference between sex-related values and between peak VO_2 values measured on the cycle ergometer versus the treadmill. Pearson correlations were used to assess the relationship between two isolated variables. A $p < 0.05$ was considered statistically significant.

An approach for modeling the relationship between age and VO_2 values was performed by a simple linear regression.

RESULTS AND DISCUSSION

Figure 1 illustrates the selection procedure. After a preliminary search, 1,283 articles were retrieved, and 131 were considered potentially relevant based on the title and abstract contents; only 114 were eligible for full text evaluation. Out of these, 94 trials were excluded for several reasons specified in the figure, leaving 20 reports which contained complete information relevant for this review; these were accordingly chosen for final analysis.

Included studies were published from 1985 to 2011, comprising a total of 3,808 children.

General study descriptions are shown in Table 1 indicating ergometer used, patients' details, age and maturation evaluation (type of evaluation if there was any), BMI, peakHR and VO_2 values.[20-39]

Among all included trials, 12 studies (60%) used the Tanner-Whitehouse evaluation scale to analyze children's maturation.[20] One study chose the Weber method,[21] whereas one identified the sample as pre-menarchal and therefore this analysis considered the population as pre-pubertal.[23] The remaining 7 trials provided no evaluation of maturation, as shown in 1.

Overall, children were 9.1 ± 1.8 years old. Those children who were evaluated as pre-pubertal in their original trials were 9.6 ± 1.9 years old. Seven articles provided no pre-pubertal evaluation of the included children; these were significantly younger (8.4 ± 1.9) than children in the other studies. No correlation was found between age and VO_2 values (Figure 2).

Most of the studies (12 trials, 60%) used a treadmill to perform the cardiopulmonary test. Seven studies (35%) used a cycle ergometer to perform the CPX. Only one trial compared cardiopulmonary values between both types of ergometers.[24]

All trials mentioned the criteria used to evaluate the maximal testing level. Sixteen trials[21-25,38-39] chose more than one of the following methods for maximal CPX consideration: (i): exhaustion in 17 trials (85%); (ii) very

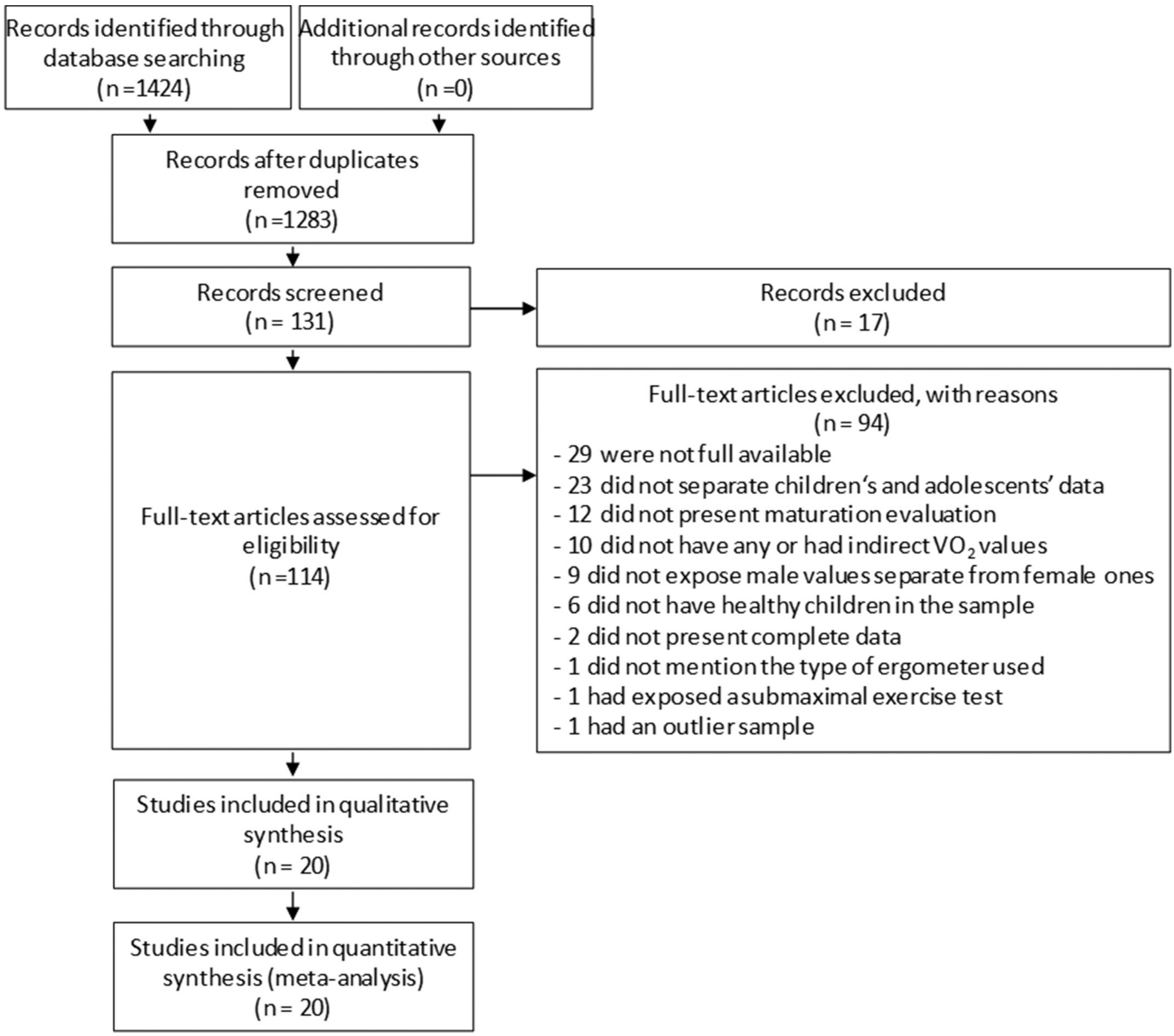

Figure 1 - Search Strategy. Results of search and selection of articles for final analysis.

high respiratory exchange ratios equal to 1(11 trials), or to 0.99 (3 trials) in 14 studies (70%); (iii) estimated HR peak in 14 trials (70%); (iv) VO_2 plateau when VO_2 rise was less than 2 mL/kg/min despite continued increase in workload in three trials (15%).

In those reports in which CPX was executed on the cycle ergometer, the children were instructed to maintain a constant pedaling rate around 70/minute.

Confidence intervals and means of peak VO_2 values are presented in Figure 3. Details from collected data according to each ergometer are shown in Table 2, which also contains age, BMI, peak RH, and peak VO_2 confidence intervals from the trials according to sex. Table 3 shows the differing values from CPX cycle ergometer and treadmill data.

On subgroup analysis, there was a statistically significant difference of 13% in VO_2values for male vs. female, but no difference between ergometers).

Analyzing peak VO_2 in mL/min, i.e., with no weight assumption, a similarity between female and male children was observed as well: females had 1.3 ± 0.2 mL/min and males1.4 ± 0.3 mL/min.

VO_2 values for girls on the cycle ergometer were the lowest values of all and were not correlated with peak HR values. Female pre-pubertal children who had a respiratory exchange ratio (RER) < 1 had a minimum peak VO_2 of 40.4 ± 5.6, a mean peak VO_2 of 42.3 ± 5, and a maximum peak VO_2 of 44.2 ± 4.6, with no statistical differences. Female pre-pubertal children who had an RER > 1 had similar minimum,

Table 1 - Overall characteristics of trials included in this review

Author(ref)	Ergometer	Sex	N	Age	Maturation evaluation	BMI (kg/m^2)	Peak HR (BPM)	peak VO_2 (ml/min/kg)
Reybrouck[20]	treadmill	M/F	67	5-11	Weber	NA	NA	42-51
Sunnegardh[21]	Cycle	M/F	63	8	NA	16	206/207	46-53
Washington[22]	Cycle	M/F	50	8	NA	16	196/196	42-47
Rowland[23]	Treadmill	F	12	11.5	premenarch	18	203	51
Armstrong[24]	Cycle/treadmeill	M/F	314	10-12	Tanner	16-19	NA	39-51
Welsman[26]	Treadmill	M/F	146	9	Tanner	NA	193-207	43-53
Trowbridge[27]	Treadmill	M/F	75	7-8	NA	NA	192-199	36-47
Welsman[28]	Treadmill	M/F	32	10	Tanner	20	201-212	52-62
Armstrong[29]	Treadmill	M/F	120	11-12	Tanner	17	201-202	43-48
Rump[30]	Treadmill	M/F	17	7.4	NA	15-16	203-205	49-56
Vinet[31]	Cycle	M/F	35	10	Tanner	18	200-203	41-48
Gürsel[32]	Treadmill	M/F	48	8-10	NA	NA	169-190	35-39
Eiberg[33]	Treadmill	M/F	609	6-10	NA	16	196-199	44-49
Dencker[34]	Cycle	M/f	477	9-10	Tanner	18	NA	35-42
Arngrímsson[36]	Cycle	M/F	10-13	9	Tanner	17-19	NA	42-50
Kolle[37]	Cycle	M/f	1291	9	NA	18	NA	42-48
Dencker[38]	Treadmill	M/F	436	6-7	Tanner	16	197-199	44-49
McNarry[39]	Treadmill	F	10	12	Tanner	19	NA	40

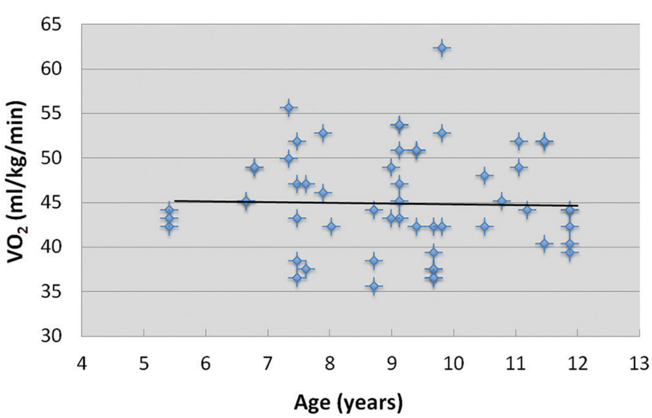

Figure 2 - A register of the linear regression of oxygen consumption (VO_2: mL/min/Kg) over age in children 5 - 12 years old: The R^2 regression coefficient (0.0006) indicates that VO_2 is not a function of age.

mean, and maximum peak VO_2 results: 38.7 ± 4.1; 40.8 ± 4.3; 42.8 ± 4.7, respectively, with no statistical differences.

BMI values correlated inversely to peak VO_2 values for overall data ($r = 0,4$; $p < 0.05$). Female subjects on cycle ergometer also exhibited an inversed correlation of BMI with peak VO_2 ($r = -0.68$; $p < 0.05$).

Peak HR values during CPX averaged 5.4 bpm above the estimated 95% maximal HR (196.9 ± 8 versus 191.5 ± 1.2, respectively), indicating that these were in fact maximal tests. Estimated maximal heart rates derive from the equation $HR_{max} = 208 - [0.7 \times age]$.[22] Statistically significant, this peak HR value correlated with peak VO_2 value in the treadmill data ($r = 0.68$ for male and $r = 0.78$ for female); the same correlation occurred for male children on the cycle ergometer ($r = 0.53$).

Systolic and diastolic blood pressure values were only reported in one study;[22] thus, no analysis could be made in this meta-analysis.

To the best of our knowledge, this is the first meta-analysis of expected CPX values in pre-pubertal children with an age-homogenous sample; thus, many factors were taken into consideration for analysis: VO_2 values similarities for sexes, maturation evaluation, criteria for test interruption, influence of body mass index upon VO_2, and the interaction between VO_2 and ergometer type.

In all of the selected reports, CPX was never performed to help in decision-making regarding therapeutics, because only healthy children were involved. Reports relating to the use of the test date back to more than 4 decades;[20] therefore, CPX has been shown to be a safe tool for evaluating physical performance and physiological limitations for this population.[40]

A large number of trials provided no data on the evaluation of maturation when analyzing children. Even though seven studies did not mention any type of maturation evaluation, they were included in this meta-analysis, because the average age of these children was 8.2 years old, meaning that they were significantly younger than those who had in fact been evaluated. Therefore, these studies were included in this meta-analysis because they had consistently investigated pre-pubertal children.

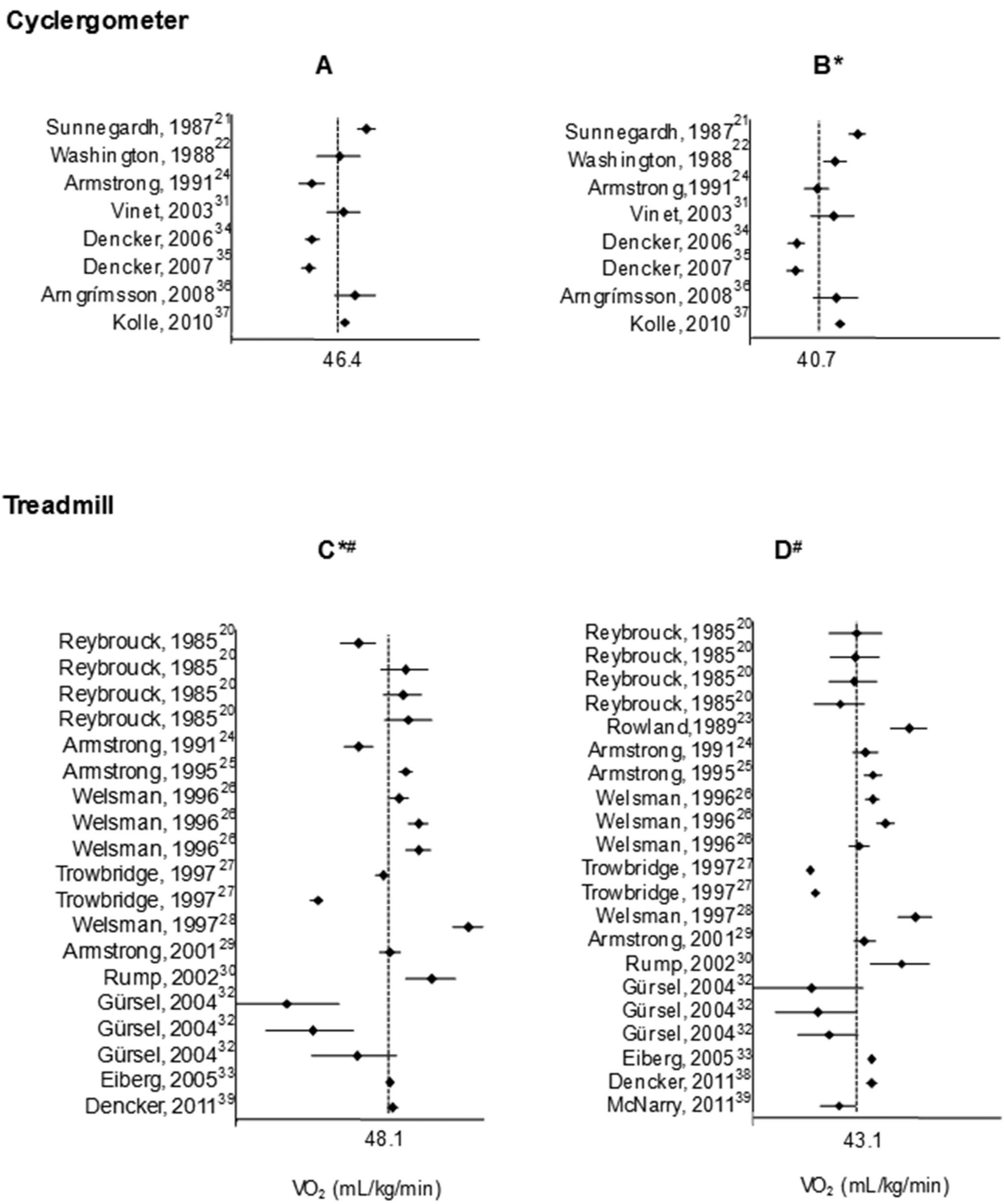

Figure 3 - Forest Plot of VO_2 log odds ratio. A: Male VO_2 value on cycle ergometer; B. Female VO_2 value on cycle ergometer; C: Male VO_2 value on treadmill; D: Female VO_2 value on treadmill. * $p < 0.05$ comparing female cycle ergometer VO_2 to male treadmill VO_2; # comparing male treadmill VO_2 to female treadmill VO_2

Table 2 - Comparison of demographic and CPX parameters, regarding sex

	Age (years)	BMI	peak HR (bpm)	Min peak VO_2 (mL/min/Kg)	Mean peak VO_2 (mL/min/Kg)	Max peak VO_2 (mL/min/Kg)
Total	9.1 ± 1.8	17.2 ± 1.3	196.9 ± 8.9	42.5 ± 6.0	44.9 ± 5.7	47.4 ± 5.8
Male	9.1 ± 1.7	17.1 ± 1.2	194.7 ± 9.3	45.1 ± 6.3	47.6 ± 5.8	50.1 ± 5.8
Female	9.2 ± 1.9	17.2 ± 1.4	191.5 ± 1.2	40.0 ± 4.7	42.4 ± 4.3	44.8 ± 4.6

BMI: Body mass index; CPX: Cardiopulmonary exercise testing; HR: Heart rate; min: minim; max:maximal; VO_2: Oxygen consumption (mL/min/Kg).

Table 3 - Comparison of demographic and CPX parameters, regarding ergometers

	Cyclergometer			Treadmill		
	Total	Male	Female	Total	Male	Female
Age (years)	9.5 ± 1.3	9.5 ± 1.4	9.6 ±1.3	9.0 ± 1.9	8.9 ± 1.7	9.1 ± 2.1
BMI	17.2 ± 1.2	17.3 ± 1.2	17.1 ± 1.1	17.1 ± 1.4	16.8 ± 1.2	17.3 ± 1.5
peak HR (bpm)	200.5 ± 6.2	191.3 ± 1.0	200.2 ± 5.6	196.2 ± 9.3	193.7 ± 9.7	198.5 ± 8.6
Min peak VO_2 (mL/min/Kg)	41.4 ± 4.5	44.1 ± 3.9	38.8 ± 3.4*	42.9 ± 6.6	45.5 ± 7.1*#	40.5 ± 5.1#
Mean peak VO_2 (mL/min/Kg)	43.6 ± 4.8	46.4 ± 4.2	40.7 ± 3.5*	45.4 ± 6.0	48.1 ± 6.4*#	43.1 ± 4.5#
Max peak VO_2 (mL/min/Kg)	45.7 ± 5.3	48.8 ± 4.9	42.6 ± 3.9*	48.0 ± 6.0	50.7 ± 6.3*#	45.6 ± 4.6#

BMI: Body mass index; CPX: Cardiopulmonary exercise testing; HR: Heart rate; min: Minim; max: Maximal; NM: Nonmentioned; VO_2: Oxygen consumption (mL/min/Kg). *$p < 0.05$ comparing female cycle ergometer VO_2 to male treadmill VO_2; # comparing male treadmill VO_2 to female treadmill VO_2.

Many maturation-dependent traits respond in different ways to physiological stress induced by physical exercise and show differences in peak VO_2 from pre-puberty and post-puberty.[41-44]

Firstly, the pubertal stage is associated with a period of insulin resistance.[45] In fact, children have 50-60% of the muscle glycogen found in adults. Children have lower lactate dehydrogenase activity with higher pH and higher adenosine triphosphate levels during muscle contraction.[46] This is because children rely more heavily on aerobic metabolism as fuel when compared with adults. They also rely more heavily on lipid[46-48] and less on carbohydrate use for energy.[46,49] Children also recover more rapidly after exercise,[47,50] which may favor activities that are more aerobic in nature than those that are of a brief duration and/or of a higher intensity.[49,50]

Secondly, the total muscle mass of children compared with their total body mass is almost 10% less than that of adults,[48,51] and their motor unit recruitment patterns differ during exercise.[46] Children also have lower ventilation, which is compensated by a significantly higher arterial-mixed venous O_2 difference to achieve the same or similar VO_2 rates.[46,52]

Because of all these differences in physiological responses, it is important to consider children separately from teens and adults.

The Tanner-Whitehouse scale is based on the development of secondary sexual characteristics, such as breast development and menarche in girls, standards for the penis in boys and pubic hair development in both sexes.[41] This scale is the most common method of maturity assessment; it is feasible and simple, meaning that trained staff are apt to apply it and to have access to the data. The lack of a sexual maturity assessment is the reason why trials that combined information about children, adolescents, and adults were not included in this study.

Regarding differences in gender, this review showed that there were significant disparities between girls and boys on the treadmill. Although there are studies which also show that boys achieve greater distances on CPX[52,53] and higher VO_2 values as a result of improved cardiorespiratory efficiency and a greater muscle-to-weight ratio,[53-55] final conclusions have not reached a consensus about these differences,[38,52-54] because it has also been reported that girls have approximately the same peak VO_2 per kg of lean body mass as boys do;[27,32,56] therefore, peak VO_2 was not correlated to BMI itself.[27,32] Our findings support this last conclusion. Although female values of peak VO_2 (in mL/min/Kg) on the cycle ergometer were the only ones that correlated with BMI, female values were the same when VO_2 was analyzed as mL/min (with no relation to weight mass). This lack of correlation might have happened because the analyzed sample was very homogenous according to BMI values.

In regard to the comparison between the treadmill and the cycle ergometer, the peak VO_2 values difference on the cycle ergometer vs. treadmill was not supported by the research data from adults, whose anaerobic threshold, HR, and peak VO_2 are 10% higher on the treadmill vs. the cycle ergometer.[56-60]

Reports also point out that a cycle ergometer test may require an average of 10 additional minutes to achieve maximal effort than tests on treadmills,[61] because (i) subjects on the cycle ergometer have an inability to keep up with their performance;[61-63] (ii) a greater activation of large amounts of muscle mass occurs during a treadmill test;[58,59,61] (iii) more discomfort in the thigh muscles occurs during the cycle ergometer test; (iv) less intensity of effort and protocol duration to maximize aerobic energy transfer is achieved on the cycle ergometer.[57,59,61]

The 18-20% differences on peak VO_2 values found in this analysis were similar to the 22% difference reported elsewhere;[61] however, smaller differences have also been reported: 7%,[61] 8%,[24,64] or 12% higher on a treadmill.[61,65] The best way to confirm differences between ergometers would be by pairing the sample and randomizing tests on different days. Although two trials studied both ergometers,[24,64] only one of them had a paired evaluation, showing no differences between ergometers.[64]

The reason for the discrepancies between findings in this analysis and the findings of the earlier studies is unclear because the collected tests had been analyzed as maximal tests. Although in published studies, 50% of the subjects achieved maximal CPX values,[61] in this analysis we were unable to guarantee that maximal CPX was indeed reached due to the lack of data for HR, BP, and time in more than 40%,95%, and 95% of the selected studies of this current meta-analysis, respectively. In spite of this lack of data, it is possible to state that the maximal observed heart rates were higher the the 95% of maximal expected rates, as previously noted.[62]

LIMITATIONS

This review would be richer if more CPX parameters (RER levels, time of the test, SBP, DBP, HR) had been presented in the original trial reports. The lack of values such as time and blood pressure, for example, limited the current analysis.

CLINICAL IMPLICATIONS

The parameters found in the CPX for healthy children can be helpful in arriving at more precise diagnoses, in assessing the severity of impairment, in determining the response to treatment, and in predicting mortality for ill children.

CONCLUSION

Given the present data, the mean peak VO_2 value for pre-pubertal children was considered to be 45.7±5.9 L/min/kg, also considering a 20% difference in peak VO_2 value between boys and girls.

CONFLICT OF INTEREST

Authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Tavares, AC carried out the study concept, design, acquisition of data, analysis and interpretation of data, draft of initial manuscript, manuscript revision, submission and approval of final manuscript version to be published; Bocchi, EA reviewed and approved final manuscript version to be published; Teixeira Neto, IS carried out the acquisition of data, draft of the manuscript, manuscript review, and approved final manuscript version to be published; Guimarães GV supervised data collection and approved final manuscript version to be published.

ACKNOWLEDGMENTS

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo - FAPESP (2001/08985-0).Guilherme V Guimarães (CNPq # 304733/2008-3) was supported by Conselho Nacional de Pesquisa.

METANÁLISE DE TESTES DE EXERCÍCIOS CARDIOPULMONARES EM CRIANÇAS PRÉ-PÚBERES SAUDÁVEIS

O objetivo do trabalho foi analisar dados relativos à função cardiopulmonar e capacidade funcional em crianças saudáveis submetidas a ergoespirometria. Uma revisão meta-analítica sistemática de ergoespirometria em crianças foi realizada com base na literatura indexada no PubMed, Bireme, e Embase. Os parâmetros pesquisados foram: idade, sexo, índice de massa corporal, avaliação da maturação, tipo de ergômetro utilizado para ergoespirometria, e os valores cardiopulmonares relacionados (frequência cardíaca máxima e consumo máximo de oxigênio [VO_2]). Vinte artigos foram selecionados, que incluíram 3808 crianças, com uma média de 9,1 anos de idade. Esteiras erogmétricas foram utilizadas em 55% dos ensaios, e bicicletas erogmétricas em outros 45% incluídos nesta análise. Os seguintes resultados estatisticamente significantes foram encontradas: em análise de subgrupo, valores de VO_2 de pico em meninos, obtidos na esteira foram 20% maiores do que os respectivos valores em meninas na bicicleta ergométrica; valores de VO_2 pico em meninos na esteira foram 18% maiores do que para meninas no mesmo ergômetro. O Índice de massa corpórea correlacionou-se inversamente com VO_2 de pico na análise total e em meninas testadas em ciclo-ergômetro. A frequência cardíaca máxima durante o teste ergo-espirométrico foi 5,6 BPM superior aos 95% da freqüência cardíaca máxima prevista. A maior parte dos parâmetros ergo-espirométricos não havia sido relatada nos estudos originais por nós analisados. A conclusão desta metanálise é que o valor de VO_2 de pico para crianças pré-púberes é cerca de 18% maior nos meninos versus meninas e em esteira vs. ciclo-ergômetro.

PALAVRAS-CHAVE: função cardiopulmonar, teste cardiopulmonar, consumo máximo de oxigênio

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