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REVIEW

Reference values for cardiopulmonary exercise testing in healthy subjects – an updated systematic review

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ABSTRACT

Introduction: Reference values for cardiopulmonary exercise testing (CPET) parameters provide the comparative basis for answering important questions concerning the normalcy of exercise responses in patients, and significantly impacts the clinical decision-making process.

Areas covered: The aim of this study was to provide an updated systematic review of the literature on reference values for CPET parameters in healthy subjects across the life span.

A systematic search in MEDLINE, Embase, and PEDro databases were performed for articles describing reference values for CPET published between March 2014 and February 2019.

Expert opinion: Compared to the review published in 2014, more data have been published in the last five years compared to the 35 years before. However, there is still a lot of progress to be made. Quality can be further improved by performing a power analysis, a good quality assurance of equipment and methodologies, and by validating the developed reference equation in an independent (sub)sample. Methodological quality of future studies can be further improved by measuring and reporting the level of physical activity, by reporting values for different racial groups within a cohort as well as by the exclusion of smokers in the sample studied. Normal reference ranges should be well defined in consensus statements.

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Cardiopulmonary exercise testing; healthy adults; healthy children; exercise physiology; reference values; maximal oxygen consumption; aerobic capacity; VO_{2max}

1. Introduction

Cardiopulmonary exercise testing (CPET) is an important diagnostic tool for assessing aerobic fitness of individuals [1]. Although many different exercise testing protocols are employed to estimate aerobic fitness [2], the gold standard for objectively assessing aerobic fitness remains cardiopulmonary exercise testing (CPET) during which respiratory gas exchange, ventilatory, and heart rhythm measurements are continuously performed throughout an incremental exercise intensity until voluntary exhaustion [3]. As such, CPET provides an evaluation of the integrative exercise response of the cardiovascular, respiratory, and metabolic systems to an incremental work rate [4]. This relatively non-invasive, dynamic physiologic test permits the evaluation of resting, submaximal, and peak exercise responses, as well as recovery responses, providing the clinician relevant information for clinical decision-making [4]. Examples concerning the usefulness of CPET for clinical decisions are the evaluation of exercise intolerance [4], eligibility for organ transplantation, and preoperative risk stratification [5].

Adequate reference values provide the comparative basis for answering important questions concerning the normality of exercise responses, and can significantly impact the clinical decision-making process [6,7]. As recommended by the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) guideline, each exercise laboratory must select an appropriate set of reference values that best reflects the characteristics of the population tested, and the equipment, protocol, and methodology utilized to collect the reference values [4]. Many reference values for different CPET parameters obtained in different populations are available in the literature. We have previously published a systematic review of reference values for CPET parameters published up to 2014 [8]. The current article is an update of our previous publication, including recent papers, as well as an extension towards the pediatric population. Reference values for pediatric CPET published up to 2014 were previously reviewed by Blais et al. [9]. The aim of this study was to provide an updated systematic review of the literature on reference values for CPET parameters in healthy subjects across the life span.

2. Methods

This systematic review of the literature followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

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Article highlights

- There is no single set of ideal reference values; population characteristics of each population are too diverse to pool data in a single equation.
- Each exercise laboratory must select an appropriate set of reference values that best reflect the characteristics of the (patient) population tested, and equipment and methodology utilized.
- Adequate reference values provide the comparative basis for answering important questions concerning the normalcy of exercise responses in patients, and can significantly impact the clinical decision-making process.
- Researchers, end-users, and industry should collaborate to establish a continuous development and update of reference values for CPET parameters using an open source database technology. There is a growing number of geographic regions in which reference values are established: Europe, Japan, South America, and Scandinavia were most frequently studied regions. Data from other regions such as other Asian countries, Middle East, and Africa are needed.
- Reference values for CPET parameters may change over time and should be regularly updated and/or validated.
- Standardization of the methodology to generate reference values, reporting of CPET parameters, reporting on specific software and hardware settings of the equipment, and data harmonization are necessary to facilitate interpretation and to optimize the clinical applications of CPET.

2.1. Data sources and search strategy

A search strategy was created and critically reviewed and approved by experienced exercise physiologists with the support of a medical librarian. After approval, published articles in the electronic databases MEDLINE, Embase, and PEDro were searched up to February 2019 (articles published from March 2014). We used the systematic search strategy as described in Appendix A. The search strategy did not have any limitations on ethnicity and language. Relevant reference lists were hand-searched as a method to supplement electronic searching.

2.2. Selection of studies

Results of the searches in different electronic databases were combined, where after duplicates were removed by two reviewers (CM and DP). The same two reviewers screened all unique records for potential relevance using the title, abstract or descriptors, or both. Hereafter, remaining articles were screened by the two reviewers on compliance with the eligibility criteria based on the full-text of the articles. Reasons for possible article exclusion based on its full-text were recorded.

2.3. Eligibility criteria

Studies with the objective to evaluate reference values for maximal CPET were included. Furthermore, inclusion criteria were: studies that included healthy subjects (no age restriction), studies using cycle or treadmill ergometry for CPET, cross-sectional studies or cohort studies, and studies that reported CPET parameters. Exclusion criteria were: studies published before March 2014, studies of which the full-text was not available, intervention studies, studies in which no maximal exercise protocol was used, and studies that exclusively included elite athletes.

2.4. Data extraction

All authors extracted data using a standard data extraction form. Data extraction was performed in pairs of reviewers (TT and MB, CM and DP, EH and WB), and discrepancies in extracted data were discussed with an independent reviewer (BB) till consensus was reached. If data were missing or further information was required, serious attempts were made to contact the corresponding authors to request for further information.

2.5. Methodological quality

Methodological quality of the selected studies was assessed using a quality list as provided in the ATS/ACCP guideline (see Appendix B) [4]. This list is a combination of study requirements to obtain an optimal set of reference values as described in the ATS/ACCP guideline and the code number scheme of shortcomings and limitations. Each criterion was scored as 'yes', 'no', or 'don't know', with one point for each 'yes'. A study was considered to be of high quality when it scored ≥10 points (≥75% of the maximum score of 14), of moderate quality when it scored 7 to 9 points, and of low quality when it scored ≤6 points. Quality assessment of all studies was performed in pairs of reviewers as well, and discrepancies in the scoring of criterions were discussed till consensus was reached. There was no blinding on authors or journal.

3. Results

3.1. Selected studies

We identified 578 potential studies published between March 2014 and February 2019. After initial screening, 125 studies were regarded potentially eligible. After reading the full-text, 29 studies were considered eligible for inclusion. A flowchart displaying exact details of the selection process, including the reasons for exclusion, is presented in Figure 1.

3.2. Study characteristics

Table 1 depicts the overall study characteristics. The 29 included studies assessed 87.256 subjects in total, of which were 54.214 males and 33.042 females. Age of included subjects ranged between 6 and 90 years. CPET was performed using a cycle ergometer in 14 studies (48.3%) and using a treadmill in 14 studies (48.3%), whereas one study (3.4%) used both modalities. There was a wide variety in the used CPET protocols, in which all studies used a continuous stepwise or ramp incremental protocol. Included studies included data from three different continents, of which most represented countries were European (n = 16), North-American (n = 9), and South-American (n = 5). Sample size ranged from 38 to 18.189 subjects. Sixteen studies (55.2%) were performed in adults, eight studies (27.6%) in children, and five studies

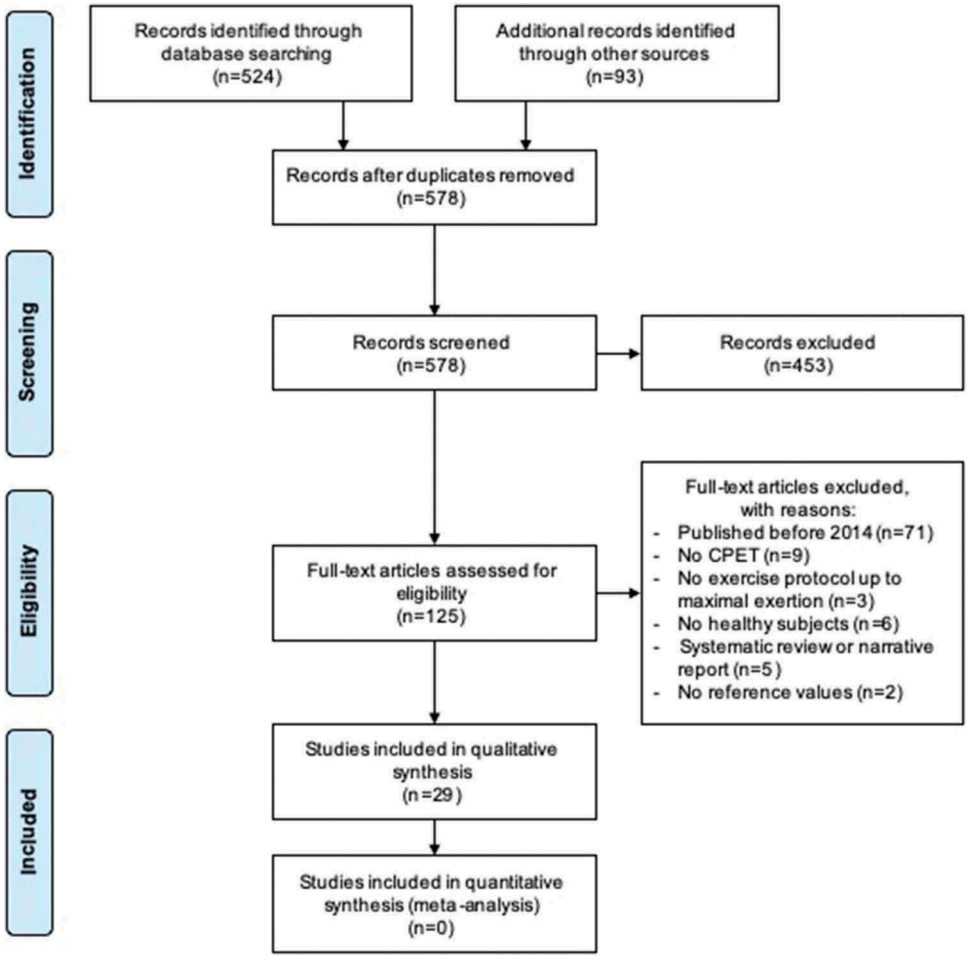

Figure 1. The PRISMA flow diagram displaying the selection of studies and reasons for exclusion.

(17.2%) in a combined sample. Some of the publications included CPET data from the same core database (e.g. FRIEND database, LowLands Fitness Registry).

3.3. Methodological quality assessment

Quality of the included studies varied, and none of the studies fulfilled all 14 quality criteria. A 'quality score' ≥10 was seen in 4 studies, 15 studies received a score of 7 to 9, and 11 studies received a score of ≤6. Frequently observed weaknesses were a lack of power analysis, quality assurance of equipment and methodologies, and reference equation validation. Table 2 provides a detailed overview of the methodological score of the included studies on the ATS/ACCP quality list [4].

3.4. Meta-analysis

Each of the included studies has various numbers of shortcomings and limitations, which are noted in Table 2. Meta-analysis of the data was not meaningful, as a large heterogeneity of methods and subjects (including sampling bias, uneven quality of primary data, and inadequate statistical treatment of the data) was observed.

3.5. Results of individual studies

Table 3 shows reference values for cardiovascular, ventilatory, and ventilatory efficiency parameters. Studies differed in the way of reporting reference values. Studies that did report reference values using regression equations are included in Table 3. Several studies reported their reference values in tables. We refer to these specific tables of the respective study for further details.

3.6. Cardiovascular parameters

3.6.1. Oxygen uptake at peak exercise

Twenty-six studies reported oxygen uptake at peak exercise (VO_{2peak}) in L/min, mL/min, or in mL/kg/min [11–28], but not all studies provided reference values. Several different parameters were used to predict VO_{2peak}. Body height, body mass, age, and sex were often included in prediction equations. VO_{2peak} (absolute values) increased with body height and body mass, was lower in females, decreased with age during adulthood, but increased with age during childhood.

3.6.2. Ventilatory anaerobic threshold

Only one study in children reported ventilatory anaerobic threshold (VAT) values [29], no study reported VAT values in

Table 1. Overall study characteristics.

Reference	Sample size (males/females)	Age (years)	Sample characteristics	Country	Smokers included	Treadmill or cycle ergometry	Protocol	Primary parameters measured	Methodology	Time averaging (s)
Aadland 2016	765 (402/363)	20–85	Population-based, retrospective	Norwegian	Yes	TM	Modified Balke protocol	VO_2, HR, RER	Gas analyzer	30 s
Abella 2016	215 (138/77)	6–17	Hospital-based, retrospective	Argentina	?	TM	Bruce protocol	VO_2[a], HR, RER, O_2-pulse, VE/VCO_2-slope, SpO_2	B × B	10–60 s
Agostini 2017	500 (260/240)	18–77	Population-based, prospective	Italy	Yes	CY	Personalized incremental ramp protocol	VO_2, CO, arteriovenous oxygen difference, HR, SV, CI	B × B	20 s
Almeida 2014	3119 (1624/1495)	8–90	Hospital-based, retrospective	Brazil	Yes	TM	Personalized incremental ramp protocol	HR, SBP, DBP, RER, VE, VO_2	B × B	20 s
Blanchard 2018	228 (112/116)	12–17	Population-based, prospective	Canada	No	CY	Personalized incremental ramp protocol	VO_2, O_2-pulse, WR[a], VE, HR, RER, OUES, OUES-slope below VAT, VE/VCO_2-slope, VE/VCO_2-slope below VAT, VE/VCO_2 at VAT, VO_2/WR-slope, O_2-pulse/WR-slope, HRR[c]	B × B	?
Bongers 2015	214 (114/100)	8–19	Population-based, prospective	The Netherlands	?	CY	Godfrey protocol (10, 15, or 20 W/min)	WR, HR, RER, VO_2[a], VE, VE/VCO_2-slope, OUES, OUEP, OUE at VAT	B × B	30 s
Buys 2014	1411 (877/534)	20–60	Population-based, prospective	Belgium	?	CY	Incremental protocol (20 W/min)	VO_2, WR, HR, RER, OUES	B × B	30 s
Dilber 2015	164 (99/65)	11–17	Hospital-based	Croatia	?	TM	Bruce protocol	WR[1], HR[a,b], RER, VO_2[a], O_2-pulse[a,b], $\Delta VO_2/\Delta WR$, SBP[a,b], BF[a,b], VT[a,b], VE[a], VE/VO_2[a], VE/VCO_2[a], VD/VT[a], $PETCO_2$[a]	B × B	15 s
Duff 2017	70 (33/37)	10–18	Population-based, prospective	Canada	?	TM	Incremental TM protocol (start at 2.0 mph, 1%, increase of 0.5 mile/hr/min)	VO_2, VE, HR, RER	B × B	15 s
Genberg 2016	181 (90/91)	50	Population-based, prospective	Sweden	Yes	CY	Incremental protocol (10 W/min, with initial work rate of 30 W (women) and 50 W (men)	WR, VO_2[a], VE/VCO_2 at VAT	B × B	?
Herdy 2015	3922 (2388/1534)	15–74	Hospital-based, prospective	Brazil	No	TM	Personalized incremental ramp protocol	VO_2	Mixing chamber gas analyzer	10 s
Hossri 2018	217 (69/148)	4–21	Hospital-based, retrospective	Brazil	?	TM	Personalized incremental ramp protocol	OUES, $PETCO_2$ at rest, VE/VCO_2-slope, VAT, O_2-pulse, RER, SpO_2[2]	Gas analyzer	30 s
Kaafarani 2017	184 (113/71)	6–18	Hospital-based, retrospective	The Netherlands	No	CY	Godfrey protocol (10, 15, or 20 W/min)	VO_2, WR, RER, SBP	B × B	30 s
Kaminsky 2015[d]	7783 (4611/3172)	20–79	Population-based, retrospective	United States	?	TM	Personalized incremental ramp protocol	VO_2, HR, RER	Gas analyzer	20–30 s
Kaminsky 2017[d]	4494 (1717/2777)	20–79	Population-based, retrospective	United States	?	CY	Personalized incremental ramp protocol	WR, HR, RER	Gas analyzer	20–30 s
Kaminsky 2018[d]	5232 (3043/2189)	20–79	Population-based, retrospective	United States	?	TM	Personalized incremental ramp protocol	VE, VO_2, HR[2], SBP at rest, DBP at rest	Gas analyzer	20–30 s
Kokkinos 2018[d]	5100 (3378/1722)	20–79	Random, population-based, retrospective	United States	Yes	CY	?	VO_2	Open circuit spirometry	30–60 s

(*Continued*)

Table 1. (Continued).

Reference	Sample size (males/females)	Age (years)	Sample characteristics	Country	Smokers included	Treadmill or cycle ergometry	Protocol	Primary parameters measured	Methodology	Time averaging (s)
Lintu 2014	140 (71/69)	9–11	Hospital-based, retrospective	Finland	?	CY	Incremental (1 W/6 s, with initial work rate of 20 W)	WR, VO_2, VE, RER, VE/VCO_2 (lowest), O_2-pulse, HR[b,c], SBP[b,c]	B × B	15 s
Loe 2014	3512 (1758/1754)	20–90	Random, population-based, prospective	Norway	Yes	TM	Incremental (0.5–1.0 km/h/min or 1–2% incline)	WR[a], HR[a], VO_2[a], VE[a], BF[a], VT[a], VCO_2[a], RER[a]	B × B	?
Meyers 2017[d]	7759 (4601/3158)	20–79	Population-based, retrospective	United States	?	TM	Personalized incremental ramp protocol	VO_2, HR, RER, SBP, DBP	?	20–30 s
Mylius 2019	4477 (3570/907)	7–65	Population-based, retrospective	The Netherlands	No	CY	Personalized incremental ramp protocol	VO_2	B × B	30–60 s
Neto 2019	18189 (12555/5634)	13–69	Population-based, retrospective	Brazil	?	TM	Personalized incremental protocol	VO_2	B × B	30 s
Ozemek 2017	2644 (1510/1134)	18–76	Population-based, retrospective	United States	No	TM	Bruce, modified Bruce, BSU Bruce ramp, Balke, modified Balke, and personalized incremental protocol	VO_2, HR[b]	Open circuit spirometry	?
Pistea 2016	99 (58/41)	>70	Population-based, prospective	France	Yes	CY	Incremental 10, 15, 20, 25, or 30 W/min (depending on subjects age, body mass, and physical fitness level)	VO_2, HR[b], WR, VE[b], VE/VCO_2, VE/VO_2, RER	B × B	20 s
Rapp 2018	10090 (6462/3628)	21–83	Population-based, retrospective	Germany	Yes	CY	Ramp protocol + multistage protocols	VO_2, SBP, DBP	B × B	10 s
Sabbahi 2018[d]	2736 (1525/1211)	20–79	Random, population-based, retrospective	United States	?	TM	?	SBP[b], DBP[b], HR	NA	NA
Stensvold 2017	310 (150/160)	70–77	Random, population-based, prospective	Norway	Yes	CY/TM	10 W/30 s, on CY, or incremental protocol on TM	HR[c], VO_2[a], RER[a], VCO_2[a], BF[a], VE[a], BR, VT, O_2-pulse, VE/VO_2[a], VE/VCO_2[a], SBP, DBP	B × B	Average of three highest consecutive values
Tompouri 2017	38 (18/20)	9–11	Hospital-based, prospective	Finland	?	CY	Incremental 1 W/6 s, with initial work rate of 20 W	WR[a], VO_2[a,b], RER	B × B	15 s
van de Poppe 2018	3463 (2868/595)	20–60	Population-based, retrospective	The Netherlands, Belgium	No	CY	Personalized incremental ramp protocol	WR, VO_2, HR, RER	B × B	30 s

If not explicitly stated, a variable was obtained at peak exercise.

B × B = breath-by-breath; BF = breathing frequency; BR = breathing reserve; CI = cardiac index; CO = cardiac output; CY = cycle ergometry; DBP = diastolic blood pressure; HR = heart rate; HRR = heart rate reserve; NA = not applicable; O_2-pulse = oxygen-pulse; O_2-pulse/WR-slope = relation between oxygen-pulse and work rate; OUE = oxygen uptake efficiency; OUEP = oxygen uptake efficiency plateau; OUES = oxygen uptake efficiency slope; $PETCO_2$ = end tidal carbon dioxide pressure; RER = respiratory exchange ratio; s = seconds; SBP = systolic blood pressure; SpO_2 = peripherally measured oxygen saturation; SV = stroke volume; TM = treadmill ergometry; VAT = oxygen uptake at the ventilatory anaerobic threshold; VCO_2 = carbon-dioxide production; VD/VT = physiologic dead space to tidal volume ratio; VE = minute ventilation; VE/VCO_2 = minute ventilation to carbon dioxide production ratio; VE/VCO_2-slope = relationship between minute ventilation to carbon dioxide production; VE/VO_2 = minute ventilation to oxygen uptake ratio; VO_2 = oxygen uptake; VO_2/WR-slope = relation between oxygen uptake and work rate; $\Delta VO_2/\Delta WR$ = delta oxygen uptake to delta work rate ratio (oxygen cost of work); VT = tidal volume; WR = work rate; ? = unknown.

[a]: Variable(s) also obtained at the VAT; [b]: Variable(s) also obtained at rest; [c]: Variable(s) also obtained during recovery; [d]: data from the FRIEND registry.

Table 2. Methodological quality of the included studies list based on the ATS/ACCP guidelineappendi.

Reference	A/P	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total score
Aadland 2016	A	0	1	0	0	1	0	0	0	1	1	1	1	1	1	9
Abella 2016	P	0	0	0	0	1	0	0	0	0	1	1	0	0	0	3
Agostini 2017	A	1	0	0	0	1	0	0	1	0	1	1	1	0	1	7
Almeida 2014	A + P	0	1	0	0	1	1	0	0	0	1	1	0	1	0	6
Blanchard 2018	P	1	1	0	1	1	0	0	1	0	1	1	1	0	1	9
Bongers 2016	P	1	0	0	0	1	0	0	1	1	1	1	1	0	1	8
Buys 2014	A	1	0	1	0	1	1	0	1	1	1	1	1	1	1	11
Dilber 2015	P	0	0	0	0	1	0	0	?	0	1	1	0	0	0	3
Duff 2017	P	1	0	0	0	0	1	0	1	1	1	1	0	0	0	6
Genberg 2016	A	1	1	0	0	1	1	1	1	1	1	1	0	0	0	9
Herdy 2016	A + P	1	1	0	1	1	1	0	1	0	1	1	0	1	1	10
Hossri 2018	A + P	0	0	0	0	1	1	0	0	0	0	1	1	0	1	5
Kaafarani 2017	P	1	0	0	1	1	0	0	0	1	1	1	1	0	1	8
Kaminsky 2015	A	1	0	0	0	1	1	1	0	1	0	1	1	0	1	8
Kaminsky 2017	A	1	0	0	0	1	1	1	0	1	0	1	1	0	1	8
Kaminsky 2018	A	1	0	0	0	1	1	1	0	1	0	1	1	1	1	9
Kokkinos 2018	A	1	0	0	0	1	1	1	0	1	1	0	1	1	1	9
Lintu 2015	P	0	0	0	1	1	1	0	0	0	1	1	0	0	1	6
Loe 2014	A	1	0	0	0	1	1	1	1	1	1	1	0	0	1	9
Myers 2017	A	1	0	0	0	1	1	0	0	1	1	1	1	1	1	9
Mylius 2019	A + P	1	0	0	1	1	1	0	0	1	1	1	1	1	1	10
Neto 2019	A + P	1	0	0	0	1	1	0	0	1	1	1	1	0	1	8
Ozemek 2017	A	1	0	0	0	1	1	0	0	0	1	1	0	0	1	6
Pistea 2016	A	0	1	0	0	1	0	0	1	0	1	1	0	0	0	5
Rapp 2018	A	1	0	0	1	1	1	0	0	1	1	1	1	0	1	9
Sabbahi 2017	A	1	0	0	0	1	1	0	0	1	1	1	1	0	0	7
Stensvold 2017	A	1	1	0	0	1	1	0	1	1	1	1	1	0	1	10
Tompuri 2017	P	1	1	0	1	1	0	0	1	0	1	1	0	0	1	8
van de Poppe 2018	A	1	0	0	1	1	1	0	0	1	1	1	1	1	1	10

See appendix B for the methodological quality list based on the ATS/ACCP guideline.
A=adult subjects; P=pediatric subjects, 0= criterion is not met, 1= criterion is not met.

adult subjects. Reference values for VAT (mL/min) increased with body height and body mass in children and were provided for male and female subjects separately.

3.6.3. Heart rate at peak exercise

One study in children [29] and one study performed in adults [30] provided prediction equations for heart rate at peak exercise (HR_{peak}). The pediatric study reported four different equations, two for males, and two for females. Body height, body mass, and age were predictors of HR_{peak} [29]. Six prediction equations for HR_{peak} in adults were reported using both cross-sectional and longitudinal data. Males had a higher HR_{peak} during young adulthood compared to females; however, males showed a somewhat faster decline in HR_{peak} values with age compared to females [30].

3.6.4. Oxygen pulse

One study [29] performed in children provided four different equations for peak oxygen pulse (O_2-pulse), two for males, and two for females. No study reported O_2-pulse reference values in adults.

3.6.5. Blood pressure

One study [31] performed in children provided two prediction equations for systolic blood pressure at peak exercise. Systolic blood pressure increased with attained work rate at peak exercise (WR_{peak}), and the increment in systolic blood pressure was independent of age and sex. There was no study that provided reference values in adults for systolic blood pressure at peak exercise.

3.6.6. Work rate at peak exercise

Two studies [29,32] reported equations for the attained WR_{peak} during CPET. These studies reported 18 different equations for the prediction of WR_{peak}. In adults, WR_{peak} increased with body height, body mass, and was significantly higher in male subjects. In children, WR_{peak} increased with the development of body height and body mass (Table 3).

3.7. Ventilatory parameters

3.7.1. Minute ventilation at peak exercise

Ten studies [29,33–41] reported data for minute ventilation at peak exercise (VE_{peak}). Almost all studies reported VE_{peak} data using tabulated data. Two sex-specific prediction equations were provided for children [29]. One prediction equation was provided for adults [37], in which VE_{peak} values were lower in females and declined with age throughout adulthood.

3.7.2. Tidal volume at peak exercise

Four studies [29,35,39,41] reported reference values for tidal volume at peak exercise (TV_{peak}). Two studies were performed in children [29,35] and two in adults [39,41]. One study [29], performed in children, provided a prediction equation for TV, the other studies provided tabulated data.

3.7.3. Breathing frequency at peak exercise

Two studies [35,41] reported breathing frequency at peak exercise (BF_{peak}). One study [35] was performed in children and one in older adults (70–77 years of age) [35]. Results were only provided in tabulated data.

Table 3. Reference values of the included studies for cardiovascular parameters, ventilatory parameters, and ventilatory efficiency parameters.

Variable	Reference	Age-range	Sex	Prediction equation or reference data	R^2, SEE
Cardiovascular parameters					
VO_{2max}/VO_{2peak} (mL/kg/min)	Aadland 2016	<55	M	VO_{2max}/VO_{2peak} = 22.04 + (−0.18 × age (years)) + (−0.13 × body mass (kg)) + (2.61 × time to exhaustion (min))	?,4.46
VO_{2max}/VO_{2peak} (mL/kg/min)	Aadland 2016	>55	M	VO_{2max}/VO_{2peak} = 40.05 + (−0.27 × age (years)) + (−0.13 × body mass (kg)) + (1.49 × time to exhaustion (min))	?,3.91
VO_{2max}/VO_{2peak} (mL/kg/min)	Aadland 2016	<55	F	VO_{2max}/VO_{2peak} = 23.03 + (−0.15 × age (years)) + (0.10 × body mass (kg)) + (1.95 × time to exhaustion (min))	?,3.87
VO_{2max}/VO_{2peak} (mL/kg/min)	Aadland 2016	>55	F	VO_{2max}/VO_{2peak} = 39.67 + (−0.25 × age (years)) + (0.13 × body mass (kg)) + (1.07 × time to exhaustion (min))	?,3.19
VO_{2max}/VO_{2peak} (mL/kg/min)	Almeida 2014	8–90	M/F	VO_{2max}/VO_{2peak} = 53.478 + (−7.518 × sex) + (−0.254 × age) + (0.430 × BMI) + (6.132 × physical activity)	0.679,?
VO_{2max}/VO_{2peak} (mL/kg/min)	Kokkinos 2018	20–79	M/F	VO_{2max}/VO_{2peak} = 1.74 × (WR_{peak} × 6.12/body mass (kg)) + 3.5	
VO_{2max}/VO_{2peak} (mL/kg/min)	Kokkinos 2018	20–79	M	VO_{2max}/VO_{2peak} = 1.76 × (WR_{peak} × 6.12/body mass (kg)) + 3.5	
VO_{2max}/VO_{2peak} (mL/kg/min)	Kokkinos 2018	20–79	F	VO_{2max}/VO_{2peak} = 1.65 × (WR_{peak} × 6.12/body mass (kg)) + 3.5	
VO_{2max}/VO_{2peak} (mL/kg/min)	Myers 2017	20–79	M/F	VO_{2max}/VO_{2peak} = 79.9 − (0.39 × age) − (13.7 × sex (0 = male; 1 = female) − (0.127 × body mass (lbs))	0.62, 7.2
VO_{2max}/VO_{2peak} (mL/min)	Blanchard 2018	12–17	M	VO_{2max}/VO_{2peak} = (−0.297 × body height^2) + (105.9 × body height) + (36.6 × corrected body mass) + (0 × age) + −8660	
VO_{2max}/VO_{2peak} (mL/min)	Blanchard 2018	12–17	F	VO_{2max}/VO_{2peak} = (−0.24 × body height^2) + (86.8 × body height) + (14.7 × corrected body mass) + (0 × age) + −6424	
VO_{2max}/VO_{2peak} (mL/min)	Blanchard 2018	12–17	M	Z-score = VO_{2peak} _ [(−0.3 × body height^2) + (105.88 × body height) + (36.59 × body mass) + (−8660.14)]/(6.35 × body height) + (−717.05)	
VO_{2max}/VO_{2peak} (mL/min)	Blanchard 2018	12–17	F	Z-score = VO_{2peak} _ [(−0.24 × body height^2) + (86.856 × body height) + (14.7 × body mass) + (−6424.42)]/(2.12 × body height) + (−45.9)	
VO_{2max}/VO_{2peak} (mL/min)	Mylius 2019	7.9–65	M	VO_{2max}/VO_{2peak} = −2537.29 + 743.35 + (24.3 × body height) + (12.57 × body mass) + (spline function for age: estimate degrees of freedom: 4.263, reference degrees of freedom 5.260)	0.57, 556.5
VO_{2max}/VO_{2peak} (mL/min)	Mylius 2019	7.9–65	F	VO_{2max}/VO_{2peak} = −2537.29 + (24.3 × body height) + (12.57 × body mass) + (spline function for age: estimate degrees of freedom: 7.391, reference degrees of freedom 8.288)	0.57, 556.5
VAT (mL/min)	Blanchard 2018	12–17	M	VAT = (−0.146 × body height^2) + (56.3 × body height) + (18.0 × corrected body mass) + (−48.3 × age) + −3898	
VAT (mL/min)	Blanchard 2018	12–17	F	VAT = (−0.00407 × body height^2) + (−2.14 × body height) + (15.9 × corrected body mass) + (−26.7 × age) + 1282	
VAT (mL/min)	Blanchard 2018	12–17	M	Z-score = VAT _ [(−0.13 × body height^2) + (52.37 × body height) + (17.21 × body mass) + (−51.9 × age) + (−3565.48)]/(3.24 × body height) + (−109.49)	
VAT (mL/min)	Blanchard 2018	12–17	F	Z-score = VAT _ [(−0.004 × body height^2) + (−2.14 × body height) + (15.91 × body mass) + (−26.72 × age) + (1281.8)]/(0.45 × body height) + (215.33)	
HR_{peak} (beats/min)	Ozemek 2017	18–76	M	HR_{peak} = (−0.005 × age^2) − (0.33 × age) + 205 (cross-sectional)	0.386
HR_{peak} (beats/min)	Ozemek 2017	18–76	F	HR_{peak} = (0.0002 × age^3) − (0.02 × age^2) + (0.44 × age) + 191 (cross-sectional)	0.358
HR_{peak} (beats/min)	Ozemek 2017	18–76	M/F	HR_{peak} = (0.0002 × age^3) − (0.02 × age^2) + (0.44 × age) + 211 (cross-sectional)	0.369
HR_{peak} (beats/min)	Ozemek 2017	18–76	M	HR_{peak} = −0.83 × age + 215 (longitudinal)	BIC provided
HR_{peak} (beats/min)	Ozemek 2017	18–76	F	HR_{peak} = −0.74 × age + 211 (longitudinal)	BIC provided
HR_{peak} (beats/min)	Ozemek 2017	18–76	M/F	HR_{peak} = (0.0002 × age^2) − (0.03 × age^2) + 0.84 + 185 (longitudinal)	BIC provided
HR_{peak} (beats/min)	Blanchard 2018	12–17	M	HR_{peak} = (−0.000532 × body height^2) + (0.313 × body height) + (−0.259 × corrected body mass) + (0 × age) + 169.5	
HR_{peak} (beats/min)	Blanchard 2018	12–17	F	HR_{peak} = (−0.0213 × body height^2) + (7.198 × body height) + (−0.193 × corrected body mass) + (−0.809 × age) + −391.1	

(*Continued*)

Table 3. (Continued).

Variable	Reference	Age-range	Sex	Prediction equation or reference data	R^2, SEE
HR_{peak} (beats/min)	Blanchard 2018	12–17	M	Z-score = HR_{peak} – [(–0.0005 × body height^2) + (0.31 × body height) + (–0.26 × body mass) + (169.45)]/(0.1 × body height) + (–7.47)	
HR_{peak} (beats/min)	Blanchard 2018	12–17	F	Z-score = HR_{peak} – [(–0.02 × body height^2) + (7.2 × body height) + (–0.19 × body mass) + (–0.81 × age) + (–391.11)]/(–0.12 × body height) + (28.41)	
O_2-pulse$_{peak}$ (mL/beat)	Blanchard 2018	12–17	M	O_2-pulse$_{peak}$ = (–0.00131 × body height^2) + (0.459 × body height) + (0.214 × corrected body mass) + (0 × age) + –37.48	
O_2-pulse$_{peak}$ (mL/beat)	Blanchard 2018	12–17	F	O_2-pulse$_{peak}$ = (–0.00019 × body height^2) + (0.075 × body height) + (0.1007 × corrected body mass) + (0 × age) + –1.83	
O_2-pulse$_{peak}$ (mL/beat)	Blanchard 2018	12–17	M	Z-score = O_2-pulse$_{peak}$ – [(–0.001 × body height^2) + (0.41 × body height) + (0.2 × body mass) + (–0.2 × age) + (–35.14)]/(0.03 × body height) + (–2.69)	
O_2-pulse$_{peak}$ (mL/beat)	Blanchard 2018	12–17	F	Z-score = O_2-pulse$_{peak}$ – [(–0.0002 × body height^2) + (0.07 × body height) + (0.1 × body mass) + (–1.83)]/(–0.003 × body height) + (2.17)	
Blood pressure (mm Hg)	Kaafarani 2017	6.2–18.6	M/F	Normality SBP = 0.00004 × ($WR_{peak}{}^2$) – 0.00526 × (WR_{peak}) + 0.46541 Mean SBP = 0.2853 × (WR_{peak}) + 111.46	
WR_{peak} (W)	Blanchard 2018	12–17	M	WR_{peak} = (–0.0182 × body height^2) + (–5.324 × body height) + (2.824 × corrected body mass) + (4.170 × age) + 378.9	
WR_{peak} (W)	Blanchard 2018	12–17	F	WR_{peak} = (–0.06025 × body height^2) + (20.57 × body height) + (0.741 × corrected body mass) + (0 × age) + –1622	
WR_{peak} (W)	Blanchard 2018	12–17	M	Z-score = WR_{peak} – [(–0.02 × body height^2) + (–5.32 × body height) + (2.82 × body mass) + (–4.17 × age) + (378.86)]/(0.22 × body height) + (–7.62)	
WR_{peak} (W)	Blanchard 2018	12–17	F	Z-score = WR_{peak} – [(–0.06 × body height^2) + (20.57 × body height) + (0.74 × body mass) + (–1622.29)]/(–0.28 × body height) + (–24.41)	
WR_{peak} (W)	Poppe 2018	20–60	M/F	WR_{peak} = –102 + (1.5 × body mass (kg)) + (1.9 × body height (cm)) – (2.0 × age) – (sex × 60 (M:1; F:0))	0.57, 44.2
WR_{peak} (W)	Poppe 2018	20–60	M	WR_{peak} = (–0.967 × age^2) + (5.2057 × age) + 257.12	0.99
WR_{peak} (W)	Poppe 2018	20–60	M	WR_{peak} = (–0.0372 × body mass^2) + (8.0074 × body mass) – 92.929	0.99
WR_{peak} (W)	Poppe 2018	20–60	M	WR_{peak} = (0.0162 × body height) – (2.4774 × body height) + 227	0.99
WR_{peak} (W)	Poppe 2018	20–60	F	WR_{peak} = (–0.0012 × age^3) + (0.1147 × age^2) ¯ (4.7471 × age) + 278.7	0.99
WR_{peak} (W)	Poppe 2018	20–60	F	WR_{peak} = (0.002 × body mass^3) ¯ (0.4715 × body mass^2) + (38.12 × body mass) – 818.6	0.99
WR_{peak} (W)	Poppe 2018	20–60	F	WR_{peak} = (–0.0642 × body height^2) + (24.481 × body height) – 2101.7	0.99
WR_{peak} (W/kg)	Poppe 2018	20–60	M/F	WR_{peak} = 2.45 – (0.026 × body mass (kg)) + (0.024 × body height (cm)) – (0.024 × age) – (sex × 0.84 (M: 1; F: 0])	0.4,0.54
WR_{peak} (W/kg)	Poppe 2018	20–60	M	WR_{peak} = (–0.0008 × age^2) + (0.0247 × age) + 3.9059	0.99
WR_{peak} (W/kg)	Poppe 2018	20–60	M	WR_{peak} = (7E-06 × body mass^3) + (0.0016 × body mass^2) + (0.109 × body mass) + 2.022	0.99
WR_{peak} (W/kg)	Poppe 2018	20–60	M	WR_{peak} = (–4E-07 × body height^4) + (0.0003 × body height^3) – (0.083 × body height^2) + (9.8777 × body height) – 435.9	0.99
WR_{peak} (W/kg)	Poppe 2018	20–60	F	WR_{peak} = (–0.0005 × age^2) + (0.0139 × age) + 3.2404	0.99
WR_{peak} (W/kg)	Poppe 2018	20–60	F	WR_{peak} = (–0.0004 × body mass^2) + (0.029 × body mass) + 2.8378	0.99
WR_{peak} (W/kg)	Poppe 2018	20–60	F	WR_{peak} = (–0.0009 × body height^2) + 0.31 × body height) – 24.466	0.99
Ventilatory parameters					
VE_{peak} (L/min)	Almeida 2014	8–90	M/F	VE_{peak} = 75.32 ± 15.78 (range 33.10–121.9) Tabulated data (n = 2495)	SD provided
VE_{peak} (L/min)	Blanchard 2018	12–17	M	Z-score = VE_{peak} – [(–0.002 × body height^2) + (–0.42 × body height) + (0.98 × body mass) + (3.17 × age) + (2.7)]/[(0.4 × body height) + (–52.54)]	

(*Continued*)

Table 3. (Continued).

Variable	Reference	Age-range	Sex	Prediction equation or reference data	R^2, SEE
VE_{peak} (L/min)	Blanchard 2018	12–17	F	Z-score = VE_{peak} − [(−0.007 × body height^2) + (2.56 × body height) + (0.53 × body mass) + (1.13 × age) + (−202.86)]/[(0.07 × body height) + (3.72)]	
VE_{peak} (L/min)	Bongers 2016	8–18	M	VE_{peak} = 80 ± 25 (range 42–157) Tabulated data (n = 114)	SD provided
VE_{peak} (L/min)	Bongers 2016	8–18	F	VE_{peak} = 71 ± 21 (34–152) Tabulated data (n = 100)	SD provided
VE_{peak} (L/kg/min)	Bongers 2016	8–18	M	VE_{peak} = 1.7 ± 0.3 (0.9–2.5) Tabulated data (n = 114)	SD provided
VE_{peak} (L/kg/min)	Bongers 2016	8–18	F	VE_{peak} = 1.5 ± 0.3 (0.8–2.1) Tabulated data (n = 100)	SD provided
VE_{peak} (L/min)	Dilber 2015	11–17	M	VE_{peak} = 89.09 ± 30.1 Tabulated data (n = 99)	SD provided
VE_{peak} (L/min)	Dilber 2015	11–17	F	VE_{peak} = 67.29 ± 19.6 Tabulated data (n = 65)	SD provided
VE_{peak} (L/min)	Duff 2017	10–18	M/F	VE_{peak} = 99.2 (75.6–120.0) (median + IQR) Tabulated data (n = 70)	
VE_{peak} (L/min)	Kaminsky 2018	20–79	M/F	VE_{peak} = 17.32 − (28.33 × sex (M = 0; F = 1)) − (0.79 × age (years)) − (1.85 × body height (inches))	21.7
VE_{peak} (L/min)	Lintu 2015	9–11	M	VE_{peak} = 69.0 ± 20.0 Tabulated data (n = 71)	SD provided
VE_{peak} (L/min)	Lintu 2015	9–11	F	VE_{peak} = 63.0 ± 18.0 Tabulated data (n = 69)	SD provided
VE_{peak} (L/min)	Loe 2014	20–90	M	VE_{peak} = 123.7 ± 25.7 Tabulated data per age group	SD provided
VE_{peak} (L/min)	Loe 2014	20–90	F	VE_{peak} = 81.8 ± 17.6 Tabulated data per age group	SD provided
VE_{peak} (L/min)	Pistea 2016	>70	M	VE_{peak} = 72.77 ± 18.31 Tabulated data (n = 58)	SD provided
VE_{peak} (L/min)	Pistea 2016	>70	F	VE_{peak} = 49.50 ± 13.22 Tabulated data (n = 41)	SD provided
VE_{peak} (L/min)	Stensvold 2017	70–77	M	VE_{peak} = 96.2 ± 21.7 Tabulated data (n = 768)	SD provided
VE_{peak} (L/min)	Stensvold 2017	70–77	F	VE_{peak} = 61.1 ± 21.6 Tabulated data (n = 769)	SD provided
VT_{peak} (L)	Blanchard 2018	12–17	M	Z-score = VT_{peak} − [(0.00002 × body height^2) + (0.002 × body height) + (0.02 × body mass) + (0.09 × age) + (−1.22)]/[(0.004 × body height) + (−0.46)]	
VT_{peak} (L)	Blanchard 2018	12–17	F	Z-score = VT_{peak} − [(0.00005 × body height^2) + (−0.009 × body height) + (0.01 × body mass) + (0.06 × age) + (0.35)]/[(0.0008 × body height) + (0.17)]	
VT_{peak} (L)	Dilber 2015	11–17	M	VT_{peak} = 2.22 ± 0.6 Tabulated data (n = 99)	SD provided
VT_{peak} (L)	Dilber 2015	11–17	F	VT_{peak} = 1.84 ± 0.8 Tabulated data (n = 65)	SD provided
VT_{peak} (L)	Loe 2014	20–90	M	VT_{peak} = 2.83 ± 0.67 Tabulated data per age group	SD provided
VT_{peak} (L)	Loe 2014	20–90	F	VT_{peak} = 1.90 ± 0.43 Tabulated data per age group	SD provided
VT_{peak} (L)	Stensvold 2017	70–77	M	VT_{peak} = 2.3 ± 0.5 Tabulated data (n = 768)	SD provided
VT_{peak} (L)	Stensvold 2017	70–77	F	VT_{peak} = 1.6 ± 0.3 Tabulated data (n = 769)	SD provided
BF_{peak} (breaths/min)	Dilber 2015	11–17	M	BF_{peak} = 49.64 ± 11.7 Tabulated data (n = 99)	SD provided
BF_{peak} (breaths/min)	Dilber 2015	11–17	F	BF_{peak} = 49.49 ± 9.1 Tabulated data (n = 65)	SD provided
BF_{peak} (breaths/min)	Stensvold 2017	70–77	M	BF_{peak} = 41.8 ± 8.0 Tabulated data (n = 768)	SD provided
BF_{peak} (breaths/min)	Stensvold 2017	70–77	F	BF_{peak} = 39.7 ± 7.1 Tabulated data (n = 769)	SD provided
Ventilatory efficiency parameters					
OUEP	Bongers 2016	8–18	M	OUEP = 26.34 − (0.029 × age^2) + (1.641 × age)	0.9998
OUEP	Bongers 2016	8–18	F	OUEP = 28.437 − (0.00363 × age^2) + (1.1409 × age)	0.9999
OUES	Barron 2015	25–84	M	OUES = 0.7 − (11.51 × age) + (5.67 × body height) + (8.62 × body mass) − (49.99 × beta blocker) − (214.53 × current smoker) + (172.97 × FEV_1)	P5 and P95 provided
OUES	Barron 2015	25–80	F	OUES = −182.4 − (8.89 × age) + (10.12 × body height) + (10.51 × body mass) − (117.65 × beta blocker) − (21.45 × current smoker) + (40.31 × FEV_1)	P5 and P95 provided
OUES	Buys 2014	20–60	M	OUES = 3930 − (12.5 × age) OUES = 1093 − (18.5 × age) + (1479 × BSA)	
OUES	Buys 2014	20–60	F	OUES = 3013 − (15 × age) OUES = 842 − (18.5 × age) + (1280 × BSA)	
OUES	Bongers 2016	8–18	M	OUES = 577.2 + 6.2 × age^2 + 52 × Age	0.997
OUES	Bongers 2016	8–18	F	OUES = 342.4–2.589 × Age^2 × 214.6 × age	0.9993
OUES (10–100)	Blanchard 2018	12–17	M	Z-score = $OUES_{10-100}$ − [(−0.24 × body height^2) + (81.44 × body height) + (38.25 × body mass) + (−6176.58)]/[(9.29 × body height) + (−1137.43)]	

(*Continued*)

Table 3. (Continued).

Variable	Reference	Age-range	Sex	Prediction equation or reference data	R^2, SEE
OUES (10–100)	Blanchard 2018	12–17	F	Z-score = $OUES_{10\text{-}100}$ − [(−0.37 × body height^2) + (130.32 × body height) + (15.27 × body mass) + (−19.1 × age) + (−9 721.78)]/[(4.91 × body height) + (−474.83)]	
OUES/BSA	Hossri 2018	4–21	M/F	OUES/BSA LLN: 1200	
OUES/kg	Hossri 2018	4–21	M/F	OUES/kg ULN: 34.63	
OUES/kg	Bongers 2016	8–18	M	OUES/kg = 21.757 − (0.0011 × age^4) + (0.0562 × age^3) − (1.0675 × age^2) + (8.8991 × age)	0.9063
OUES/kg	Bongers 2016	8–18	F	OUES/kg = 41.3 + (0.0006 × age^4) + (0.0045 × age^3) + (0.3241 × age^2) + (1.4446 × age)	0.991
VE/VCO_2 at the VAT	Loe 2014	20–90	M	VE/VCO_2 = 26.7 ± 2.4 Tabulated data per age group	SD provided
VE/VCO_2 at the VAT	Loe 2014	20–90	F	VE/VCO_2 = 28.5 ± 3.6 Tabulated data per age group	SD provided
VE/VCO_2 at the VAT	Genberg 2016	50	M	VE/VCO_2 = 27.5 ± 2.70	SD provided
VE/VCO_2 at the VAT	Genberg 2016	50	F	VE/VCO_2 = 27.9 ± 3.24	SD provided
VE/VCO_2 minimum	Lintu 2015	9–11	M	VE/VCO_2 normal range: 24–32.9	SD provided
VE/VCO_2 minimum	Lintu 2015	9–11	F	VE/VCO_2 normal range: 25–33.8	
VE/VCO_2 peak	Pistea 2016	>70	F	VE/VCO_2 = 34.83 ± 5.66	SD provided
VE/VCO_2 peak	Pistea 2016	>70	M	VE/VCO_2 = 34.19 ± 4.63	SD provided
VE/VCO_2 peak	Loe 2014	20–90	M	VE/VCO_2 = 29 ± 3.3 Tabulated data per age group	SD provided
VE/VCO_2 peak	Loe 2014	20–90	F	VE/VCO_2 = 29.3 ± 4 Tabulated data per age group	SD provided
VE/VCO_2 peak	Stensvold 2017	70–77	M	VE/VCO_2 = 32.6 ± 4.4 (26.6–28.7)	P5 and P95 provided
VE/VCO_2 peak	Stensvold 2017	70–77	F	VE/VCO_2 = 31.8 ± 4.1 (26.3–38.3)	P5 and P95 provided
VE/VCO_2-slope	Abella 2016	6–17	M/F	Data shown in graph only, no equation provided	R^2 = 0.336
VE/VCO_2-slope (up to the VAT)	Dilber 2015	11–17	M	VE/VCO_2-slope = 27 ± 2.9	SD provided
VE/VCO_2-slope (up to the VAT)	Dilber 2015	11–17	F	VE/VCO_2-slope = 28.16 ± 2.8	SD provided
VE/VCO_2-slope (up to the VAT)	Blanchard 2018	12–17	M	Z-score = VE/VCO_2-slope − [(−0.0004 × body height^2) + (0.24 × body height) + (−0.1 × body mass) + (−1.01 × age) + (15.1)]/[(−0.03 × body height) + (8.71)]	
VE/VCO_2-slope (up to the VAT)	Blanchard 2018	12–17	F	Z-score = VE/VCO_2-slope − [(−0.002 × body height^2) + (0.63 × body height) + (0.06 × body mass) + (−0.31 × age) + (−24.88)]/[(−0.02 × body height) + (5.8)]	

BF_{peak} = breathing frequency at peak exercise; BMI-body mass index; BSA = body surface area; F = women; HR_{peak} = heart rate at peak exercise; IQR = interquartile range; LLN = lower limit of normal; M = men; O_2-$pulse_{peak}$ = oxygen-pulse at peak exercise; OUEP = oxygen uptake efficiency plateau; OUES = oxygen uptake efficiency slope; SBP = systolic blood pressure; SD = standard deviation; SEE = standard error of the estimate; ULN = upper limit of normal; VAT = oxygen uptake at the ventilatory anaerobic threshold; VE_{peak} = minute ventilation at peak exercise; VE/VCO_2 = minute ventilation to carbon dioxide production ratio; VE/VCO_2-slope = relation between minute ventilation and carbon dioxide production; VO_{2max} = maximal oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise; VT_{peak} = tidal volume at peak exercise; WR_{peak} = work rate at peak exercise.

3.7.4. Ventilatory efficiency parameters

3.7.4.1. Oxygen uptake efficiency plateau and oxygen uptake efficiency slope. One study [34] in children reported a reference equation for oxygen uptake efficiency plateau (OUEP). No results in adults were found. Five studies reported oxygen uptake efficiency slope (OUES) values, two in adults [42,43], two in a pediatric population [29,34], and one study reporting up to young adulthood (21 years of age) [44]. Results were reported for males and females separately. Other commonly used predictors were age, body height, body mass, or body surface area. OUES values were determined using data from 10% to 100% of the exercise test and normalized for body surface area or body mass.

3.7.5. Minute ventilation to carbon dioxide production

Minute ventilation (VE) to carbon dioxide production (VCO_2) coupling was reported in eight studies, of which four studies were performed in children [29,35,38,45] and four studies in adults [39–41,46]. VE to VCO_2 coupling was expressed in many different ways: VE/VCO_2-slope, VE/VCO_2 ratio at the VAT, the lowest VE/VCO_2 ratio during the test, or VE/VCO_2 ratio at peak exercise (see Table 3).

4. Discussion

The aim of our study was to review recently published studies in the last five years on reference values for CPET parameters in healthy children and adults. In this update of the literature, 29 studies with reference values for CPET parameters were included, in which data of 87.256 subjects (54.214 males and 33.042 females) were reported. This number is more than three times the number of subjects included in our original systematic review of the literature (25.826 subjects) [8]. This increase in number shows that the sample size of the studies is increasing over time. For an adequate interpretation of CPET, the normal range of a variety of CPET parameters (e.g. VO_{2peak}, VAT, HR_{peak}, VE/VCO_2-slope) is essential. In many studies, however, only the mean or median value for the population is provided. We recommend that studies should also report the lower and upper limit of normal. As shown in the study of Blanchard et al. [29], the use of the 80% of predicted as lower limit of normal should be abandoned. Instead, a Z-score should be used with a lower and upper limit of normal of −1.96 SD and +1.96 SD, respectively. Moreover, authors should try to statistically model their data instead of merely providing tabulated data. In addition, authors are encouraged to publish multiple different CPET parameters in one publication, such as, for example, in Bongers et al. [47]. This will help clinicians to select the optimal set of reference values for their tests. The use of reference values from different sources to interpretation one CPET will provide additional noise in its interpretation.

4.1. Comparison with previous review

Compared to our original review, more data from South America are available. In the original protocol, one study in 120 adult subjects from Brazil was available. In the last five years, four new studies from Brazil and one from Argentina were added to the literature, including the study by Neto et al. [48] among 18.189 healthy subjects between 13 and 69 years of age. These studies significantly added to the available reference values for CPET in this geographic region.

Cycle ergometry was still more commonly employed as CPET method compared to treadmill ergometry. The large variety in CPET protocols, equipment, study methodology, and parameters reported indicates the need for standardization of CPET as a clinical outcome tool. Without a robust standardization of the CPET methodology, data pooling and multi-center studies are very hard to perform.

5. Conclusion

In the last five years, 29 studies with CPET reference values of 87.256 subjects were published. We found no single set of ideal reference values, as characteristics of each population are too diverse to pool data in a single equation for each CPET parameter. Harmonization of CPET data is still urgently needed to facilitate pooling of data from different sources.

6. Expert opinion

Strength of this updated review is the inclusion of many studies from around the world with large databases. However, harmonization for CPET data is still urgently needed. Without harmonization, pooling of CPET data from different sources is hardly possible. This is well illustrated by the various parameters used for the coupling of VE and VCO_2. Many different metrics such as the ratio of the two at the VAT, at peak, or the slope are used to describe this relationship. These different metrics give all different values and thus cannot be used interchangeably.

Another limitation identified in the current review is that only a limited amount of CPET parameters are reported in the literature. An international database like the FRIEND database [49] with raw breath-by-breath data will help to report reference values for a large number of CPET parameters in a standardized manner. Using novel big data analytic methods, this database enables the continuous generation of up-to-date reference values.

The reporting of CPET reference values is still in its infancy. For instance, we recommend that in the future researchers are not only reporting the mean or median value of a population or tabulated data but obtained data should be modeled and reference ranges including upper and lower limits of normal should be provided.

Compared to the review published in 2014, more data have been published in the last five years compared to the 35 years before. However, there is still a lot of progress to be made. Quality can be further improved by performing a power analysis, a good quality assurance of equipment and methodologies, and by validating the developed reference equation in an independent (sub)sample. Methodological quality of future studies can be further improved by measuring and reporting the level of physical activity, by reporting values for different racial groups within a cohort as well as by the exclusion of smokers in the sample studied. Normal reference ranges

should be well defined in consensus statements. For example, should we use the 5th to 95th percentile or the 2.5th to 97.5th percentile as normative range? Moreover, advanced data modeling techniques should be used. Tabulated data and simple linear regression techniques should be abandoned, since they have quite large prediction errors. For example, Z-scores will provide a more qualitative analysis of the performance of a CPET parameter instead of a binary normal/abnormal.

We expect that in the near future more CPET data harmonization initiatives are undertaken to establish robust reference values for CPET. Researchers, end-users, and industry should collaborate to establish a continuous development and update of adequate reference values using an open source database technology. This database should also include longitudinal data. Using big data techniques such as curve matching, a prediction for the future development of CPET outcomes in a subject can be made. Furthermore, we expect that open source platforms for the interpretation and reporting of CPET data are developed for the harmonization of interpretation and reporting of CPET results.

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Appendix A

Search strategy

MEDLINE: ((((((((exercise test[MeSH Terms]) OR exercise test[Title/Abstract]) OR ergometry test[Title/Abstract]) OR ergometry tests[Title/Abstract]) OR Treadmill test[Title/Abstract]) OR Treadmill tests[Title/Abstract]) OR bicycle test[Title/Abstract]) OR bicycle tests[Title/Abstract])) AND ((((((((reference values[MeSH Terms]) OR reference values[Title/Abstract]) OR normal range[Title/Abstract]) OR normal ranges[Title/Abstract]) OR norms[Title/Abstract]) OR normative value [Title/Abstract]) OR normal value[Title/Abstract]) OR normal values [Title/Abstract]) OR reference ranges[Title/Abstract]) OR reference range[Title/Abstract]).

Embase: ('exercise test':ab,ti OR 'ergometry':ab,ti OR 'exercise tests':ab,ti OR 'cardiopulmonary exercise test':ab,ti OR 'cardiopulmonary exercise tests':ab,ti OR 'cardiopulmonary exercise testing':ab,ti OR 'cycle ergometry':ab,ti OR 'incremental exercise':ab,ti) AND ('values, reference':ab,ti OR 'normal range':ab,ti OR 'normal ranges':ab,ti OR 'reference values':ab,ti OR 'reference ranges':ab,ti OR 'reference range':ab,ti OR 'normal responses':ab, ti).

PEDro: 'cardiopulmonary exercise test' AND 'reference values'.

Appendix B

Modified methodological quality list according to the ATS/ACCP guidelines

Population characteristics:

(1) Subjects are community based. *(The subjects studied preferably be community bases rather than hospital based).*
(2) Level of physical activity is reported.
(3) Exclusion of different racial groups.
(4) Exclusion of smokers in the sample studied.
(5) No lack of definition of de confidence limits for individual or specified characteristics. *(Include age, sex, and anthropomorphic considerations).*

Sample size:

(6) The number of subjects tested is sufficiently equal or larger than the appropriately powered sample size, with a uniform distribution of subjects for sex and groups.
(Specific attention is given to include women and older individuals, given the changing demographics and paucity of reliable population-based CPET data for these groups).

Randomization:

(7) Randomization was applied.
(The study design includes a randomization process to avoid the potential bias seen when more physically active subjects volunteer for the study).

Design:

(8) A prospective study design

Quality assurance of equipment and methodologies:

(9) Quality control was applied.
(Quality was achieved using recommendations contained in the ATS/ACCP guidelines and the CPET protocols in accordance with recommendations specified in the ATS/ACCP guidelines).
(10) Exercise testing protocol and procedures are described.
(11) Results are obtained by either breath-by-breath analysis or mixing chamber treated in accordance with recommendation contained in the ATS/ACCP guidelines.

Treatment of data:

(12) CPET result in interval averaged, preferably every 30–60 s (to avoid the noise of shorter interval), and the peak value reported represents the mean of the last-completed stage or of all the data collected during the final stage, but preferably for no less than 30 s.

Validation:

(13) Reference equations are validated in population other than those used to generate the existing data.

Statistical treatment of data:

(14)The function that most accurately describes the distribution of the data are used. For example, curvilinear (power) functions may more accurately describe the distribution of the data. Furthermore, the precision of the individual and population predicted values are reported.