Physical activity and its correlates in people with cystic fibrosis: a systematic review

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Shareable abstract (@ERSpublications)
PwCF are as active as their healthy peers but a trend for less high-intensity PA is seen in youths with CF. This systematic review stresses the need for high-quality longitudinal studies to further unravel the PA levels of PwCF and its influencing factors. https://bit.ly/3npYkRn

Cite this article as: Kinaupenne M, De Craemer M, Schaballie H, *et al*. Physical activity and its correlates in people with cystic fibrosis: a systematic review. *Eur Respir Rev* 2022; 31: 220010 [DOI: 10.1183/16000617.0010-2022].

Received: 20 Jan 2022
Accepted: 21 June 2022

Abstract

Cystic fibrosis (CF) is a life-shortening genetic disease, affecting multiple life domains including physical activity (PA). Although higher PA levels are associated with multiple health benefits, little insight exists on the PA level of people with CF (PwCF) compared to healthy peers. Evidence on the influencing factors (*i.e.* correlates) of PA in this clinical population is scarce, but essential to fully understand their PA behaviour. Therefore, the present review aims to provide an overview of the PA level of PwCF compared to healthy peers, and the correlates of PA in PwCF. A systematic search of three databases resulted in 46 included studies. Analysis of 16 studies showed that the CF population is equally active compared to healthy peers, but there is a trend towards less high-intensity PA in youths with CF. Furthermore, PA is positively associated with quality of life, lung function, (maximal) exercise capacity, bone mineral density and quadriceps force. Also, PA was lower on weekdays compared to weekend days and lower when experiencing pulmonary exacerbations. More high-quality research is required in PwCF, particularly longitudinal studies that further explore the correlates of PA, with PA investigated as a primary outcome and measured objectively.

Introduction

Cystic fibrosis (CF) is a life-shortening hereditary multisystem disease affecting approximately one in 2000 to 3000 newborns in Europe. It is characterized by progressive lung disease, pancreatic dysfunction, elevated sweat electrolytes and male infertility [1]. Excessive viscous secretions in the lungs cause respiratory dysfunction and progressive lung function decline due to recurring infections, inflammation and airflow obstruction [2]. The disease manifests in many organs, which leads to various symptoms such as coughing and wheezing, abdominal pain, constipation, salty skin, lack of energy and muscle and joint pain [3, 4]. With the progression of the disease, symptom management requires increasing time and effort, resulting in a high therapeutic burden for the patients and their families [5]. This high therapeutic burden, together with the overall impact of the disease on people with CF (PwCF) may negatively influence their physical activity (PA) [6].

PA is defined as any bodily movement produced by the contraction of skeletal muscles resulting in a substantial increase in caloric requirements over resting energy expenditure [7]. There is overwhelming evidence on the short-term health benefits (*e.g.* higher energy levels, improved concentration and emotional well-being) and the long-term advantages (*e.g.* primary and secondary prevention of several chronic diseases and mortality) of regular PA in the healthy population [8–11].

On top of these benefits, research has suggested that there are specific health benefits for PwCF. Higher PA levels have been associated with a slower lung function decline, reduced hospitalisation, improved quality of life (QoL), nutritional status, and improved prognosis in both children and adults with CF [12–14]. Additionally, higher PA intensities, *i.e.* moderate-to-vigorous PA (MVPA) and vigorous PA (VPA), are more consistently associated with health indicators than lower intensities, *i.e.* light PA (LPA). Consequently, these higher intensities have an important long-term protective effect on health [15, 16]. In several adult populations with respiratory illness, decreased PA was shown to be a predisposing factor of greater incidence of cardiovascular disease, obesity, diabetes, cancer, dementia and physical disability [17].

The World Health Organization (WHO) published new PA guidelines in 2020, with only a limited section dedicated to populations with chronic illness in general and, to date, no CF-specific PA guidelines exist [18, 19]. Despite the WHO guidelines and the well-known benefits of regular PA, the majority of both healthy and clinical populations do not engage in the recommended amounts of PA [20, 21]. However, it remains unclear whether PwCF have different PA levels compared with healthy peers and whether PA should be targeted in interventions in this population. Importantly, a healthy lifestyle starts to evolve in early childhood, which highlights the need to explore the PA levels of children and adolescents with CF as well.

In the development of interventions and the setup of studies aiming to improve PA, knowledge on the influencing factors (*i.e.* correlates) of PA should be integrated. PA is a complex, multidimensional behaviour, subject to multiple internal and external factors [22]. In the healthy population, a wide range of PA correlates have been investigated, and the social–ecological model of health behaviour is used to categorise these correlates as either intrapersonal (*e.g.* cognitions/emotions), interpersonal (*e.g.* family and friends) or environmental factors (*e.g.* neighbourhood) [23]. Despite the excessive amount of research conducted in the healthy population, this research field is still in its infancy in the CF population.

Taking into account the limited knowledge on the PA levels of PwCF and the associated correlates, the main objective of this systematic literature review was twofold: 1) summarise the existing evidence on the PA levels of PwCF compared to healthy peers, both in youths and adults separately; 2) identify general and disease-specific correlates of PA in PwCF. Evidence gathered and summarised in this review could inform the development of future interventions to target PA in the CF population.

Methods

This systematic review is conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [24] and the protocol has been registered on PROSPERO (ID: CRD42020219169).

Information sources and search strategy

A systematic search of the literature was conducted to identify relevant studies concerning PA in CF. Both research questions were formulated using the patients–intervention–comparison–outcome (PICO) approach: 1) “How does the PA level (O) of PwCF (P) differ from healthy controls (C)?” and 2) “What are the correlates of PA (O) in PwCF (P) and what is the strength of their association?”.

Based on these PICO questions, keywords were combined using Boolean operators to formulate the following search strategy: (cystic fibrosis OR cystic fibrosis[MeSH Terms]) AND (phys* acti* OR “physical inactivity” OR “physical activity level” OR “daily living activity” OR “activities of daily living” OR physical activity[MeSH Terms] OR activities of daily living[MeSH Terms]) AND (Human). No restriction on date, study design or presence of a control group was made in the search strategy. Three electronic databases (*i.e.* PubMed, Web of Science and PsycArticles) were explored (last search 8 August 2021). Detailed information on the search strategy is provided in supplementary file E1.

Eligibility criteria and study selection

The references retrieved with the final search strategy were managed in an electronic library (*i.e.* EndNote X9). After removing duplicates, the titles, abstracts and full texts were screened by two independent reviewers. In both stages, any discrepancies were discussed or a third reviewer was asked to adjudicate. Papers were included if: 1) all subjects, or a subgroup, were diagnosed with CF; 2) PA was assessed as an outcome measure; 3) the paper included a control group of healthy individuals and/or reported correlates of PA; 4) the article was written in Dutch or English; and 5) the full text was available. There was no age restriction. Reviews, meta-analyses and animal studies were excluded. In addition, a manual search of the reference lists of the included articles was performed.

Data extraction

Data was extracted by two independent reviewers, using a pre-determined template. For the comparison between patients and healthy peers, PA outcome measures, means, standard deviations, and p-values were extracted. For the associations, the strength (R-value), if reported, and direction of the associations were collected. Authors were contacted if insufficient detail was provided in the paper, and the paper was excluded if no additional information could be delivered.

Risk of bias assessment

The risk of bias was assessed by two independent reviewers, using the Newcastle–Ottawa scale for observational studies. All articles – both cohort and cross-sectional studies – were scored with the subscale for cohorts. This eight-item checklist is subdivided into three domains: selection, comparability and outcome. Next, a level of evidence was assigned to each study following the evidence-based guideline development method. Each study was graded a level of evidence ranging from A1 up to D, depending on evidence-based medicine domain, study design and individual methodological quality. Consequently, a strength of conclusion (level 1–4) was assigned to the different outcome levels, based on the composition of the respective levels of evidence and consistency of their results. Detailed information on the risk of bias assessment can be found in supplementary file E1.

Data synthesis

An overview of the data extraction can be found in supplementary tables E2, E3 and E4. Results were split according to the two research questions and age categories: children and adolescents (referred to as youths), adults and mixed populations (*i.e.* no age restriction). The results of the first research question are summarised in figure 2 and graphically presented in figures 3 and 4. The PA behaviour of the PwCF is presented as a percentage of PA measured in the matched healthy population: (mean patient PA/mean control PA)×100. Regarding the second research question, the strength of the association, based on the reported R-value, was evaluated according to the following interpretation: poor 0.00–0.30, moderate 0.31–0.60, moderately high 0.61–0.84 and high>0.85 [25]. The interpretation of the results was performed based on the percentage of studies supporting an association with a model used in previous research as shown in supplementary table E1 [26, 27]. A meta-analysis was not performed due to the heterogeneity of study methodologies, such as the use of various PA outcome measures, *i.e.* step count, metabolic equivalent of tasks (METs) and time spent in different PA intensity levels.

Results

Study selection and characteristics

Of the 5654 studies identified through the literature search, 94 references met the inclusion criteria based on title and abstract. After evaluation of the full texts, 37 papers remained. Additionally, nine studies were added after a hand-search, which led to a total of 46 included studies. Studies were dominantly excluded from this review due to the following reasons: wrong population, outcome or study design, and language. A full PRISMA flow diagram of the screening process is shown in figure 1.

Different study designs were included: 33 cross-sectional studies of which 17 used a healthy control group, 10 longitudinal studies and three intervention studies. Of the 46 identified studies, 37% (n=17) included only children and adolescents, 35% (n=16) only adults and 28% (n=13) recruited a mixed population (*i.e.* a combination of children, adolescents and adults). 16 papers were included to answer the first research question (sample size ranging from 31 to 302 participants, with an average of 55% male participants), whereas 43 papers were included to answer the second research question (sample size ranging from 14 to 212, with an average of 49% male participants).

The methods used to measure PA varied throughout the studies, with 21 studies (46%) using objective measurements such as accelerometers (n=19) or pedometers (n=2), and 18 studies (39%) using subjective methods such as questionnaires (n=16) and interviews (n=2). In seven studies (15%), a combination of both objective and subjective measurement methods was used.

Risk of bias

The most common positively scored item was item 1 (“representativeness of the exposed cohort”) and the most common negatively scored question was item 6 (“assessment of outcome”). In summary, for the first research question, 13 studies obtained a level of evidence B, and three a level of evidence C. For the second research question, two studies obtained a level of evidence A2, seven obtained a level of evidence B and 21 a level of evidence C. Results of risk of bias assessment are provided in supplementary tables E5 and E6.

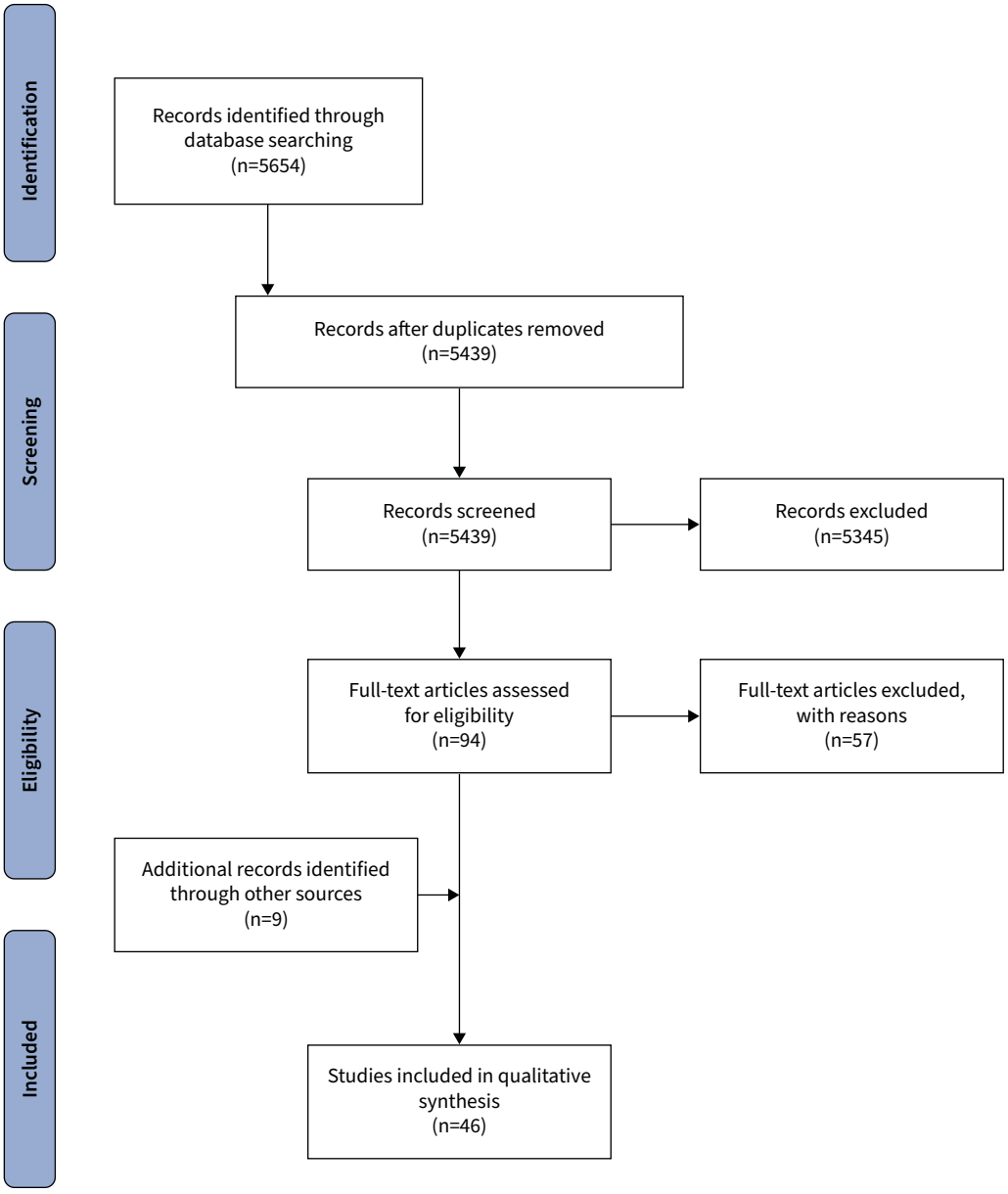

FIGURE 1 PRISMA flow diagram for database search and study selection process.

PA of PwCF compared to healthy peers

The main findings are summarised in figure 2 and graphically presented in figures 3 and 4. For detailed information, see supplementary table E3.

Total PA

Overall, nine papers reported on the total amount of PA (*i.e.* min·day^{-1}, h·week^{-1}, steps per day) of PwCF compared to healthy peers [28–36]. In youths, one study reported significantly higher total PA in CF based on accelerometry (363 *versus* 280 min·day^{-1}) [31]. No significant differences were found in the remaining studies (strength of conclusion: bias assessment level 2) [28–30, 32, 35]. In adults, one study described significantly lower self-reported PA compared to the control group (30.6 *versus* 53.2 h·week^{-1}) [29]. No significant differences were found in the other studies [33, 34, 36]. Regarding daily steps in adults, no significant differences were reported (strength of conclusion: bias assessment level 2) [33, 34, 36].

Total volume of PA, often expressed in METs, is the sum of all performed activities with their representing MET value accumulated over a specific period of time *e.g.* MET hours per week

PA outcome	Population	Significant difference		No difference	Summary n/N (%)
		↑PwCF	↓PwCF		
Total PA					
Total amount of PA (min·week^{-1}; h·day^{-1}; steps per day)	Total				1/9 (11)
	Youth	**[31]**		[28–**30**, 32, 35]	1/6 (17)
	Adult		[29]	**[33**, 34, **36]**	1/4 (25)
	Mixed	NE	NE	NE	NE
Total volume of PA (MET h·week^{-1})	Total				3/5 (60)
	Youth		[28]	[32, 35]	1/3 (33)
	Adult		[38]		1/1 (100)
	Mixed		[37]		1/1 (100)
Intensity based PA					
Average daily METs	Total				0/1 (0)
	Youth	NE	NE	NE	NE
	Adult			**[33]**	0/1 (0)
	Mixed	NE	NE	NE	NE
LPA (min·day^{-1})	Total				2/10 (20)
	Youth	**[30, 31]**	**[40]**	[35, **39, 41]**	2/6 (33)
	Adult		[38]	**[33**, 34, **36]**	1/4 (25)
	Mixed	NE	NE	NE	NE
MPA (min·day^{-1}; min·week^{-1}; h·day^{-1})	Total		NE		1/7 (14)
	Youth			**[30**, 35, **41]**	0/3 (0)
	Adult		**[36]**	**[33**, 34, 38]	1/4 (25)
	Mixed	NE	NE	NE	NE
MVPA	Total				2/7 (29)
	Youth		**[31, 40]**	**[30, 39, 41]**	2/5 (40)
	Adult			[**33**, 34]	0/2 (0)
	Mixed	NE	NE	NE	NE
VPA	Total				4/11 (36)
	Youth		[**31**, 32, **43**]	[30, 35, **41**, 42]	3/7 (43)
	Adult		**[36]**	[**33**, 34, 38]	1/4 (25)
	Mixed			**[43]**	0/1 (0)

FIGURE 2 Difference in physical activity (PA) between people with cystic fibrosis (PwCF) and healthy controls. The classification of the results was performed based on the percentage of studies supporting a difference, with the following division: 0–33, no difference; 34–59, trend for a difference; 60-100, significant difference. Yellow shading: lower for PwCF; orange shading: no difference; grey shading: trend for a difference; no shading: no evidence. Plain citation text: subjective PA measurement; bold citation text: objective PA measurement; underlined citation text: combination of subjective and objective PA measurement. LPA: light physical activity; MET: metabolic equivalent of task; MPA: moderate physical activity; MVPA: moderate-to-vigorous physical activity; n: number of studies that report a significant difference; N: number of studies that have investigated and reported on possible differences; NE: no evidence; VPA: vigorous physical activity.

(MET h·week^{-1}). This was reported in five papers [28, 32, 35, 37, 38]. In youths, one study subjectively investigated total MET h·week^{-1} and reported significantly lower activity in CF compared to healthy peers (31.4 *versus* 52.0 MET h·week^{-1}), whereas the remaining studies described no significant difference (strength of conclusion: bias assessment level 2) [28, 32, 35]. In adults, one study reported significantly lower MET minutes per week (MET min·week^{-1}) for the patient group (5307 *versus* 7808 MET min·week^{-1}) (strength of conclusion: bias assessment level 3) [38]. In a mixed population, one study showed that significantly fewer patients were categorised in the highest tertile of PA based on the International Physical Activity Questionnaire (no patients with CF *versus* six healthy controls) (strength of conclusion: bias assessment level 3) [37].

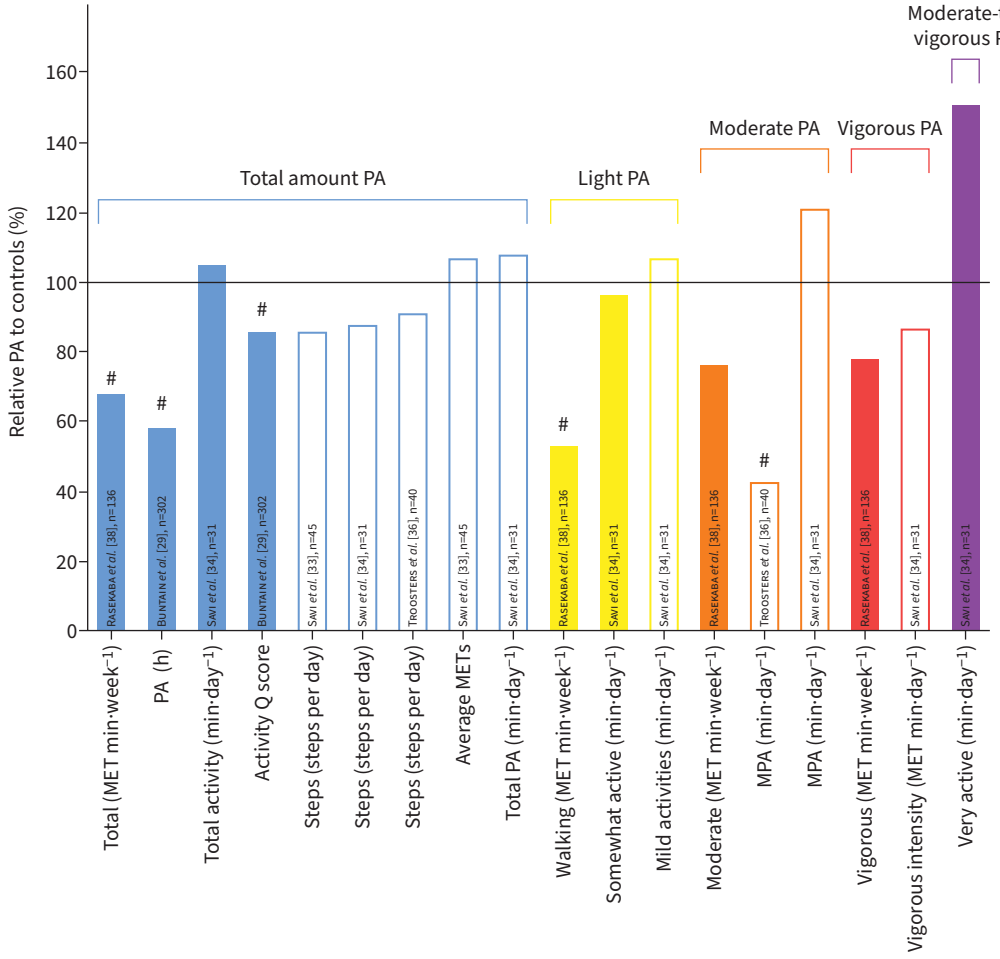

FIGURE 3 Physical activity (PA) in adults with cystic fibrosis *versus* healthy controls. Data are expressed as a percentage of PA measured in the matched healthy population. Full bars: subjectively measured PA; open bars: objectively measured PA. Outcomes are grouped based on the concept of PA that has been measured and the following colour code is used: blue, total amount of PA; yellow, light PA; orange, moderate PA; red, vigorous PA; purple, moderate-to-vigorous PA. MET: metabolic equivalent of tasks; MPA: moderate physical activity; #: significant.

Intensity-based outcome measures of PA

One study reported objectively measured average METs per minute as an indication of the global performed PA intensity per day, but found no significant difference between PwCF and healthy peers (1.77 *versus* 1.66 METs) (strength of conclusion: bias assessment level 3) [33]. Other intensity measures report time above a given intensity threshold, ranging from LPA to VPA.

LPA

10 studies investigated LPA [30, 31, 33–36, 38–41]. The evidence on LPA in youths was inconclusive as three studies reported no significant difference, two studies reported significantly higher objectively measured LPA levels (319 *versus* 226 min·day^{-1}; not reported in [30]), and one study described significantly lower LPA levels (111.5 *versus* 132.1 min·day^{-1}) (strength of conclusion: bias assessment level 3) [30, 31, 35, 39–41]. In adults, no significant difference was found for objectively measured LPA [33, 36]. In contrast, results on self-reported LPA levels are inconsistent, as one study reported non-significant differences and one study reported significantly lower MET min·week^{-1} of LPA for CF (1278 *versus* 2394 MET min·week^{-1}) (strength of conclusion: bias assessment level 3) [34, 38].

MPA, VPA and MVPA

Seven studies investigated time in MPA (min·day^{-1}, min·week^{-1}, h·day^{-1}) [30, 33–36, 38, 41]. In youths, no significant difference in MPA was found (strength of conclusion: bias assessment level 2) [30, 35, 41].

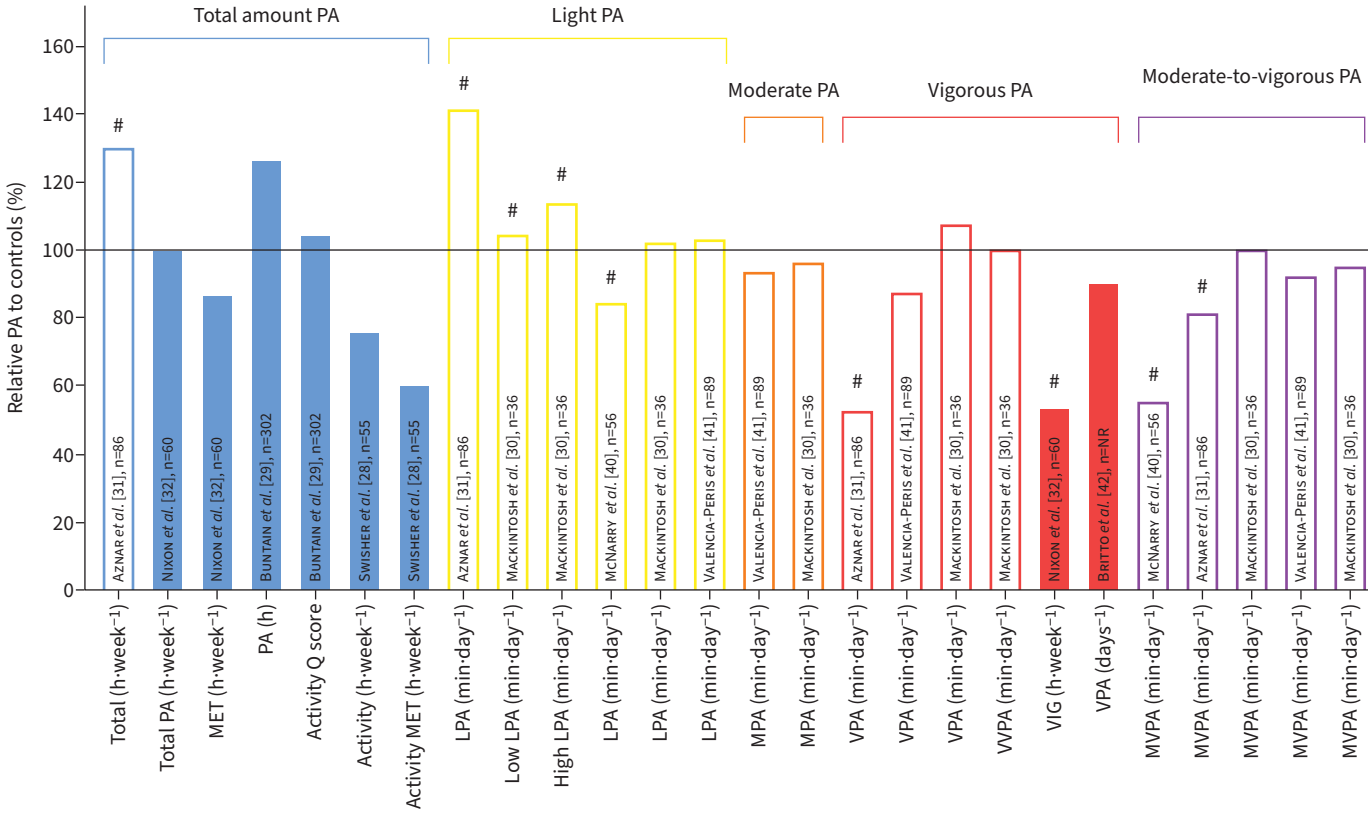

FIGURE 4 Physical activity (PA) in youths with cystic fibrosis *versus* healthy controls. Data are expressed as a percentage of PA measured in the matched healthy population. Full bar: subjectively measured PA; open bar: objectively measured PA. Outcomes are grouped based on the concept of PA that has been measured and the following colour code is used: blue, total amount of PA; yellow, light PA; orange, moderate PA; red, vigorous PA; purple, moderate-to-vigorous PA. MET: metabolic equivalents of tasks; LPA: light physical activity; MPA: moderate physical activity; MVPA: moderate-to-vigorous physical activity; (V)VPA: (very) vigorous physical activity; VIG: vigorous; Q: questionnaire; #: significant.

In adults, only one study reported significantly lower objectively measured MPA levels in CF (14.8 *versus* 34.5 min·day^{-1}) (strength of conclusion: bias assessment level 2) [33, 34, 36, 38].

Seven studies reported time in MVPA [30, 31, 33, 34, 39–41]. In youths, two studies reported significantly lower MVPA levels for CF (44 *versus* 54 min·day^{-1}; 9.6 *versus* 17.1 min·day^{-1}) (strength of conclusion: bias assessment level 2) [30, 31, 39–41]. In adults, no significant differences were found (strength of conclusion: bias assessment level 2) [33, 34].

11 studies reported time in VPA [30–36, 38, 41–43]. In youths, the evidence on VPA is inconclusive with four studies reporting no significant difference and three studies, two using accelerometers and one using a questionnaire, reporting significantly lower VPA levels (9 *versus* 17 min·day^{-1}; not reported in [43]; 2 *versus* 3.7 h·week^{-1}) (strength of conclusion: bias assessment level 3) [30–32, 35, 41–43]. In adults, three studies reported no significant differences, whereas one study using SenseWear found significantly lower VPA levels for CF (not reported) (strength of conclusion: bias assessment level 2) [33, 34, 36, 38]. In a mixed population no significant difference was found (strength of conclusion: bias assessment level 3) [43].

Correlates of PA

Correlates of PA were categorised into general and disease-specific. The most frequently studied general correlates were sex (n=19), anthropometric parameters (n=8) and age (n=5). The most frequently studied disease-specific correlates were lung function (n=15), exercise tolerance (n=11), and the influence of acute pulmonary exacerbations (n=5) on PA. Detailed information is provided in figure 5 and supplementary table E4.

General correlates

Overall, evidence on the association between sex and PA is inconsistent, with 11 studies showing higher PA levels in males and eight studies reporting no significant differences (strength of conclusion: bias

Correlate variables	Population	Related to PA		Unrelated to PA	Summary code		Strength of the association (R-value)
		Positive association	Negative association	No association	n/N (%)#	Association (+/−)¶	
General correlates							
Sex (male)	Total				11/19 (58)	?	
	Youth	[41, 48, 51, 53]		[35, 42, 44]	4/7 (57)	?	NA
	Adult	[46, 47, 50, 62]		[38, 55, 56]	4/7 (57)	?	NA
	Mixed	[43, 49, 54]		[45, 52]	3/5 (60)	+	NA
Anthrop. Para. (BMI, BMP, FFMI)	Total				3/8 (36)	?	
	Youth		[44]§	[32]	1/2 (50)	?	−0.47
	Adult	[56]	[38, 57]	[47]	2/4 (50)	?	−0.47
	Mixed			[43, 58]	0/2 (0)	0	
Age	Total				1/5 (20)	0	
	Youth		[42]	[53]	1/2 (50)	?	NA
	Adult	[38]§		[47]	1/2 (50)	?	0.55
	Mixed			[52]	0/1	0	
QoL	Total				2/3 (66)	+	
	Youth			[60]	0/1	0	
	Adult	[46]			1/1	+	NA
	Mixed	[49]			1/1	+	0.29
Weekday	Total				2/3 (66)	–	
	Youth	[30]	[59]		1/2 (50)	?	NA
	Adult		[34]		1/1	–	
	Mixed	NE	NE	NE	NE		
Disease-specific correlates							
Lung function (FEV_1)	Total				13/15 (87)	++	
	Youth	[30, 32, 51§, 53]		[44]	4/5 (80)	++	0.19–0.78
	Adult	[36, 38, 46, 56, 57, 61, 62]		[47]	7/8 (88)	++	0.18–0.72
	Mixed	[43, 52]			2/2 (100)	+	0.53
Max. exercise tolerance (peak oxygen uptake)	Total				9/11 (82)	++	
	Youth	[31, 32]		[53, 63]	2/4 (50)	?	0.35–0.83
	Adult	[33, 34, 36, 64]			4/4 (100)	++	0.32–0.55
	Mixed	[54, 65, 66]			3/3 (100)	+	0.32–0.55
Pulmonary exacerbation	Total				5/5 (100)	––	
	Youth	NE	NE	NE	NE		
	Adult		[47, 55, 62]		3/3 (100)	–	NA
	Mixed		[52, 58]		2/2 (100)	–	NA
BMD	Total				4/4 (100)		
	Youth	NE	NE	NE	NE	++	
	Adult	NE	NE	NE	NE		
	Mixed	[29, 50, 66, 67]			4/4 (100)	++	0.34–0.74
6MWT	Total				4/4 (100)	++	
	Youth	NE	NE	NE	NE		
	Adult	[34, 36, 61]			3/3 (100)	+	0.45–0.56
	Mixed	[66]			1/1 (100)	+	0.36
PI	Total				0/3 (0)	0	
	Youth			[53]	0/1 (0)	0	
	Adult			[57]	0/1 (0)	0	
	Mixed			[43]	0/1 (0)	0	
Qc force	Total				2/3 (66)	+	
	Youth	NE	NE	NE	NE		
	Adult	[36, 55]+			2/2 (100)	+	0.48–0.61
	Mixed			[58]+	0/1 (0)	0	
Infections	Total				0/3 (0)	0	
	Youth			[53]	0/1 (0)	0	
	Adult			[57]	0/1 (0)	0	
	Mixed			[43]	0/1 (0)	0	

FIGURE 5 Correlates of physical activity (PA) in people with cystic fibrosis (PwCF). When four or more studies supported an association or no association, it was coded as 00, ++ or ––, a ? was used when evidence was indeterminate. Green shading: positive association; yellow shading: negative association; orange shading: no association; grey shading: evidence is indeterminate; no shading: no evidence. 6MWT: six-minute walking test; Anthrop. Para.: anthropometric parameters; BMD: bone mineral density; BMI: body mass index; BMP: body mass percentile; FEV_1: forced

expiratory volume in 1 s; FFMI: fat-free mass index; Max.: maximal; NA: not available; NE: no evidence; PI: pancreatic insufficiency; Qc: quadriceps; QoL: quality of life. #n: number of studies that report a significant association; N: number of studies that have investigated and reported on possible associations. ¶: shows the direction of the individual/summary association. +: during exacerbation. §: only in females.

assessment level 3) [33, 35, 38, 41–56]. Furthermore, inconsistent associations were found for age and anthropometric parameters (strength of conclusion: bias assessment level 3) [32, 38, 42–44, 47, 52, 53, 56–58]. Concerning the association between weekday or weekend day and PA, evidence indicates higher PA levels during weekend days (strength of conclusion: bias assessment level 2) [30, 34, 59]. In general, evidence suggests a positive association between QoL and PA, although this was only the case in adult and mixed populations [46, 49, 60]. Higher QoL scores were associated with higher objectively and subjectively measured PA levels, although the strength of the associations were weak or not reported (strength of conclusion: bias assessment level 3) [46, 49].

Disease-specific correlates

A consistent positive association was found between lung function (*i.e.* forced expiratory volume in 1 s, FEV_1) and PA in all age groups, regardless of the PA measuring method (strength of conclusion: bias assessment level 2) [30, 32, 36, 38, 43, 44, 46, 47, 51–53, 56, 57, 61, 62]. A consistent positive association was found between (maximal) exercise capacity and PA in adult and mixed populations (strength of conclusion: bias assessment level 2) [31–34, 36, 53, 54, 63–66]. During an acute pulmonary exacerbation, all studies demonstrated decreased PA levels, which is reflected in lower total PA, MPA and step count in both adult and mixed populations (strength of conclusion: bias assessment level 2) [47, 52, 55, 58, 62]. Furthermore, PA was associated with bone mineral density (BMD) in mixed populations (strength of conclusion: bias assessment level 3) [29, 50, 66, 67]. Similarly, positive associations were reported between PA and quadriceps (Qc) force in adults; however, results were influenced by the muscle force measuring method and the patient's clinical condition [36, 55, 58]. PA was positively associated with maximal voluntary contraction, although only in stable adult patients, whereas Qc twitch force was found to be positively associated with PA in adults during acute pulmonary exacerbation (strength of conclusion: bias assessment level 2) [55]. Furthermore, no associations were found between PA and pancreatic insufficiency, the occurrence of *Pseudomonas* infection or allergic bronchopulmonary asperillosis (strength of conclusion: bias assessment level 2) [43, 53, 57].

Discussion

The present review aimed to summarise the existing evidence on the difference in PA between both youths and adults with CF and healthy peers, and to identify general and disease-specific correlates of PA in PwCF. The main findings were that PwCF engage in similar total and LPA levels compared to healthy peers. Time in M(V)PA tended to be lower, although only in youths with CF. Regarding the second research question, PA is positively associated with QoL, lung function, (maximal) exercise capacity, BMD and Qc force. Furthermore, PA levels were lower on weekdays compared to weekend days and lower when experiencing pulmonary exacerbations. Evidence on the association with sex and anthropometric parameters is indeterminate. These results should be interpreted with caution as the overall methodological quality of the studies was low.

Despite the evidence that PwCF engage in similar total and LPA levels as their healthy peers, some trends towards less time in the higher intensity spectrum of PA are seen, although only in youths with CF. It could be possible that youths with CF compensate for less time in higher intensity by spending more time doing light physically active activities, resulting in a total PA that is comparable to the healthy population. It seems plausible to explain this decrease by a greater reliance on anaerobic metabolisms when performing activities due to a reduced aerobic fitness. This results in greater lactate and carbon dioxide production which in turn stresses the ventilatory system. The discomfort associated with increased ventilation and lactate production could discourage patients to engage in more high intense activities [32]. Indeed, some studies indicate that youths with CF are already characterized by a decreased aerobic fitness compared to healthy peers [31]. This hypothesis is also supported by a comparable early decline in MVPA in pre-clinical patients with chronic obstructive disease [68]. However, it cannot be corroborated by the limited existing evidence of only four studies on MVPA levels in adults with CF, as only one reported significantly lower levels for the CF population, based on accelerometry [36]. The remaining studies collected PA data by self-report or had limited sample sizes [33, 34, 38]. More research is needed to unravel this.

Importantly, regardless of the size of this difference in M(V)PA, a vast majority of both groups do not meet the daily PA recommendation of 60 min MVPA [19]. Consequently, important health benefits are

missed. Studies on both the healthy population and other populations with respiratory diseases showed that extended periods of reduced M(V)PA result in earlier onset of obesity and adult non-communicable diseases such as cardiovascular and metabolic disease [15, 69, 70]. Over the last decades, newborn screening, nutritional therapy, pancreatic enzymes and an organised CF care have improved the nutritional status of PwCF. However, being overweight and obesity are growing concerns that enhance the need for individual medical interferences [71]. The recent progression in pharmacological therapy in PwCF has led to the development of CF transmembrane conductance regulator (CFTR) modulators. Up to 80% of PwCF are eligible for CFTR modulator therapy. These modulators improve lung function, resulting in fewer pulmonary exacerbations, and might improve pancreas function if instituted early in the disease course [72]. Studies indicated a 15% increase in FEV_1 for the newest CFTR modulator therapy, referred to as triple therapy. Regarding the (positive) influence of CFTR modulators on exercise capacity, the current evidence is limited and not yet well understood [73]. The positive impact of these modulators, combined with a lack of specialist support or changes in PwCF's usual high calorie diet, may lead to an increasing incidence of being overweight and obesity in PwCF [74]. The consequences of both the lack of sufficient MVPA and the implementation of the CFTR modulators stresses the importance of PA promotion in PwCF. PA plays an important role in the prevention of being overweight and obesity in youths, and it reduces the risk of an unhealthy weight status in adulthood [75–77]. However, the content of the PA interventions may need to be adapted to the modified clinical presentation of PwCF that are under CFTR modulator therapy. These new modulators will provide patients with the optimal physiological possibility to perform (more) PA and might render therapies less time-consuming. Despite these positive changes, PwCF are often not used to being regularly active. Therefore, their attitude towards a more physically active lifestyle will need to be tackled in these PA interventions. Importantly, 80% of PwCF are eligible for these modulators, meaning that 20% are left with their current (pharmacological) therapy. This knowledge may stimulate researchers and clinical practitioners to develop PA interventions that are personally tailored to the clinical presentation of the patient, incorporate a behavioural aspect towards an active lifestyle and start in early childhood to enhance the carry-over effect into adulthood.

To shape these interventions, deeper insight is needed into the correlates of PA in PwCF. The present review aimed to uncover the existing associations. Notably, no interpretation of the cause or effect of these associations can be made based on the cross-sectional design of most studies. Currently, the evidence (although limited) suggests a positive association between perceived QoL and PA in PwCF. This is not surprising because QoL is a multilayer concept that includes both mental and physical domains, and thus reflects the general well-being of a patient. PwCF often report their QoL as low [78]. Based on the possible link between QoL and PA, interventions dominantly targeting one of these outcomes may also positively influence the other. Furthermore, this review showed an inconsistency in results regarding the association between sex and PA in all age categories. This would suggest that future PA interventions should not differentiate between sexes. However, the healthy population shows a sex gap in PA decline during adolescence, with a greater decrease of PA in boys compared to girls [79, 80]. This trend may also be present in PwCF. Furthermore, no recommendations can be formulated on the optimal time period to implement PA interventions (*i.e.* weekday or weekend), as the evidence is indeterminate and of low methodological quality [34, 59]. More studies are necessary to establish the optimal period to implement PA interventions and to determine whether these should be sex-specific.

As one might expect, lower lung function is a sign of disease progression and is associated with less M(V)PA in CF. This finding is in agreement with the existing literature in other populations with chronic respiratory diseases [81]. To compensate the increased dead space, patients increase their minute ventilation, which may result in a greater sensation of breathlessness or discomfort, preventing patients from performing high-intensity activities [82, 83]. In addition, reduced lung function is a known risk factor for pulmonary exacerbation, that in turn has an impact on PA [84]. Pulmonary exacerbation induces a decrease in PA; however, the reversed association may not be excluded, with higher PA levels resulting in fewer pulmonary exacerbations. Several studies included in this systematic review conducted a 1-month follow-up of adults with CF during an acute pulmonary exacerbation and a stable control group and showed a significant decrease in PA in the exacerbation group [47, 55, 58, 62]. The decreased PA level recovers 1 month after exacerbation, although not to values complying with PA guidelines. The temporary drop in PA, together with the inflammation during exacerbation, results in a decline of general muscle force. However, the general muscle force of PwCF is already lower compared to healthy peers due to disease-specific abnormalities [36, 85]. Consequently, this deterioration may lead to more inactivity on the long term [86]. Studies exploring the relation between PA and muscle force showed a moderate association, suggesting that interventions targeting PA could not only focus on PA itself but may also incorporate muscle strengthening exercises. Nevertheless, more longitudinal research is needed to determine the directionality and strength of this association.

The association between (sub)maximal exercise capacity and PA is unambiguous, with only two studies reporting nonsignificant results [44, 53]. Both studies used questionnaires to estimate PA levels and were conducted in youths with a mean age of 12 years. A possible explanation is that the impact of the disease is still limited and may not have caused as much exercise intolerance yet. However, the study by Aznar *et al*. [31] included the same age category and found a positive association between peak oxygen uptake and objectively measured PA. Due to the cross-sectional character of the existing evidence, no assumptions can be made on the causality of this relationship, and, thus, no specific recommendations can be made on whether researchers should specifically focus on exercise capacity to enhance PA in PwCF. However, the association between both health outcomes is clear, and there is a tentative assumption that a certain exercise capacity is needed to give patients the possibility to perform PA at all intensities [87, 88].

Summarising the evidence and making comparisons between the existing studies is challenging because both subjective and objective PA measurement methods were used. Therefore, results from this systematic review should be interpreted with caution. Subjective methods such as questionnaires are quick, easy to use and have a low cost, but are associated with difficulties including errors in subject recall (especially for children), information provided by proxies and overestimation of PA to achieve social desirability [54, 61, 89, 90]. For this purpose, incorporating objective measures of PA should continue to be a priority in PA research. Recently, accelerometers were proven to be valid monitors to measure PA in patients with other chronic respiratory diseases [91]. Furthermore, when using objective measurement methods in research, there is a great variability in the reported PA outcomes and the methodology (*e.g.* monitoring time, number of valid days) [92]. There is evidence that a minimum of 7-day monitoring is needed to provide a reliable estimate of usual PA behaviour in youths, yet several studies only used 3–5 days of PA monitoring [93]. Additionally, extensive research has been conducted in the healthy population to develop cut-points to estimate intensities of PA based on counts per minute. Unfortunately, in the CF population, no specific guidelines on the use of these cut-points exist, resulting in a wide variability of cut-points used in CF research [94]. To tackle this issue, research with accelerometers is gradually transferring to the use of raw data instead of cut-points. However, more work is needed to address the challenges of comprehensive and consistent collecting, reporting and analysing of PA data in this patient population.

The results of the present review indicate the shortcomings of the existing evidence, which should inspire future research. PA should be studied as a primary outcome in larger high-quality, especially longitudinal, studies to provide more in-depth insight into the PA level and its correlates in PwCF. Importantly, some correlates of PA, known in the healthy population, are not yet investigated in this clinical population. For example, various behavioural factors (*e.g.* attitudes towards PA, self-efficacy and perceptions of PA) and the influence of "parental support" and "green space" remain unclear. These correlates could form excellent target points in interventions aiming to stimulate PA in PwCF.

Some limitations of this systematic review need to be acknowledged. First, only papers published in English were included. Second, the non-standardised reporting of PA outcome measures prevented the conductance of a meta-analysis. Third, a vast majority of the studies were not specifically designed to investigate PA levels, often reporting PA as a secondary outcome measure, making the interpretation of the significance of findings difficult. Strengths of the present systematic review include the broad search strategy to ensure all existing evidence was collected. A systematic review on the correlates of PA for the total CF population has not yet been published. Both significant and nonsignificant results were reported, which allows a comprehensive evaluation of the consistency and strength of the associations described.

Points for clinical practice and/or questions for future research

- Is the PA intensity of PwCF different from healthy control populations, based on objective measurements?
- Which modifiable intrapersonal factors determine PA levels of PwCF and are these different from those in a healthy population?
- Do CFTR modulator therapy influence the PA levels of PwCF?

Conclusion

In general, the CF population is as active as their healthy peers. However, in youths with CF, some tendencies towards less intense activities were found. Regarding the correlates of PA, positive associations were found with QoL, lung function, (maximal) exercise capacity, BMD and Qc force. Furthermore, PA was lower on weekdays compared to weekend days and lower when experiencing pulmonary exacerbations. Notably, the methodological quality of the included studies was limited, particularly missing objectively

measured PA data and longitudinal studies. This restricted the possibility to draw firm conclusions. Future research should focus on further unravelling the associations between PA and its influencing factors, as this knowledge is crucial in the development and implementation process of interventions aiming to stimulate PwCF to be more active (*e.g.* duration, content and modalities). This will be increasingly important to prevent obesity and its associated health risks in a growing population of PwCF on highly effective CFTR modulator therapy.

Provenance: Submitted article, peer reviewed.

Author contributions: M. Kinaupenne, M. De Craemer and H. Demeyer conceived the initial idea for this review. M. Kinaupenne selected the studies for this review, collected and analysed the data, and wrote the manuscript. M. De Craemer and H. Demeyer supported the analysis of the data and contributed to the review/editing of the manuscript. All authors reviewed the manuscript during different phases and approved the final version of the manuscript.

Support statement: H. Demeyer and M. De Craemer are senior post-doctoral researchers of Fonds Wetenschappelijk Onderzoek. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: None declared.

References

1 World Health Organization Human Genetics Programme. The molecular genetic epidemiology of cystic fibrosis: report of a joint meeting of WHO/IECFTN/ICF(M)A/ECFS, Genoa, Italy, 19 June 2002. 2004. Available from: https://apps.who.int/iris/handle/10665/68702
2 Hulzebos E, Dadema T, Takken T. Measurement of physical activity in patients with cystic fibrosis: a systematic review. *Expert Rev Respir Med* 2013; 7: 647–653.
3 Stern RC. The diagnosis of cystic fibrosis. *N Engl J Med* 1997; 336: 487–491.
4 Sawicki GS, Sellers DE, Robinson WM. Self-reported physical and psychological symptom burden in adults with cystic fibrosis. *J Pain Symptom Manage* 2008; 35: 372–380.
5 Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: Challenges to disease self-management. *J Cyst Fibros* 2009; 8: 91–96.
6 Williams CA, Stevens D. Physical activity and exercise training in young people with cystic fibrosis: Current recommendations and evidence. *J Sport Health Sci* 2013; 2: 39–46.
7 Howley ET. Type of activity: resistance, aerobic and leisure *versus* occupational physical activity. *Med Sci Sports Exerc* 2001; 33: Suppl. 6, S364–S369.
8 World Health Organization. Global recommendations on physical activity for health. 2010. Available from: www.who.int/publications/i/item/9789241599979
9 Sothern MS, Loftin M, Suskind RM, *et al.* The health benefits of physical activity in children and adolescents: implications for chronic disease prevention. *Eur J Pediatr* 1999; 158: 271–274.
10 Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006; 174: 801–809.
11 Harsha DW, Berenson GS. The benefits of physical activity in childhood. *Am J Med Sci* 1995; 310: S109–SS13.
12 Nixon PA, Orenstein DM, Kelsey SF, *et al.* The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992; 327: 1785–1788.
13 Selvadurai HC, Blimkie CJ, Cooper PJ, *et al.* Gender differences in habitual activity in children with cystic fibrosis. *Arch Dis Child* 2004; 89: 928–933.
14 Wilkes D, Schneiderman J, Corey M. Longterm effect of habitual physical activity on lung health in patients with cystic fibrosis. *Pediatr Pulmonol* 2007; 42: 358–359.
15 Booth FW, Gordon SE, Carlson CJ, *et al.* Waging war on modern chronic diseases: primary prevention through exercise biology. *J Appl Physiol* 2000; 88: 774–787.
16 Poitras VJ, Gray CE, Borghese MM, *et al.* Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. *Appl Physiol Nutr Metab* 2016; 41: Suppl. 3, S197–S239.
17 Watz H, Pitta F, Rochester CL, *et al.* An official European Respiratory Society statement on physical activity in COPD. *Eur Respir J* 2014; 44: 1521–1537.
18 Swisher A, Hebestreit H, Mejia-Downs A, *et al.* Exercise and habitual physical activity for people with cystic fibrosis: expert consensus, evidence-based guide for advising patients. *Cardiopulm Phys Ther J* 2015; 26: 108–113.
19 Bull FC, Al-Ansari SS, Biddle S, *et al.* World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020; 54: 1451–1462.

20 Shelley J, Boddy LM, Knowles ZR, *et al.* Physical activity and associations with clinical outcome measures in adults with cystic fibrosis; a systematic review. *J Cyst Fibros* 2019; 18: 590–601.
21 Tudor-Locke C, Bassett DR, Jr. How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Med* 2004; 34: 1–8.
22 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985; 100: 126–131.
23 Fleury J, Lee SM. The social ecological model and physical activity in African American women. *Am J Community Psychol* 2006; 37: 129–140.
24 Liberati A, Altman D, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; 62: e1–34.
25 Pagels P, Boldemann C, Raustorp A. Comparison of pedometer and accelerometer measures of physical activity during preschool time on 3- to 5-year-old children. *Acta Paediatr* 2011; 100: 116–120.
26 Sallis JF, Prochaska JJ, Taylor WC. A review of correlates of physical activity of children and adolescents. *Med Sci Sports Exerc* 2000; 32: 963–975.
27 Hinkley T, Crawford D, Salmon J, *et al.* Preschool children and physical activity: a review of correlates. *Am J Prev Med* 2008; 34: 435–441.
28 Swisher AK, Baer L, Bonner D, *et al.* Effect of habitual activity, lung function, and nutritional measurements on 3–minute step test performance in children with cystic fibrosis. *Cardiopulm Phys Ther J* 2004; 18: 15–20.
29 Buntain HM, Greer RM, Schluter PJ, *et al.* Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. *Thorax* 2004; 59: 149–155.
30 Mackintosh KA, Ridgers ND, Evans RE, *et al.* Physical activity and sedentary time patterns in children and adolescents with cystic fibrosis and age- and sex-matched healthy controls. *J Phys Act Health* 2018; 15: 82–88.
31 Aznar S, Gallardo C, Fiuza-Luces C, *et al.* Levels of moderate--vigorous physical activity are low in Spanish children with cystic fibrosis: a comparison with healthy controls. *J Cyst Fibros* 2014; 13: 335–340.
32 Nixon PA, Orenstein DM, Kelsey SF. Habitual physical activity in children and adolescents with cystic fibrosis. *Med Sci Sports Exerc* 2001; 33: 30–35.
33 Savi D, Di Paolo M, Simmonds N, *et al.* Relationship between daily physical activity and aerobic fitness in adults with cystic fibrosis. *BMC Pulm Med* 2015; 15: 59.
34 Savi D, Quattrucci S, Internullo M, *et al.* Measuring habitual physical activity in adults with cystic fibrosis. *Respir Med* 2013; 107: 1888–1894.
35 Kilbride E, Widger J, Hussey J, *et al.* Exercise capacity in prepubertal children with cystic fibrosis. *ISRN Pulmonology* 2012; 2012: 578240.
36 Troosters T, Langer D, Vrijsen B, *et al.* Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. *Eur Respir J* 2009; 33: 99–106.
37 Cherobin I, Dalcin P, Ziegler B. Evaluation of functional capacity and level of physical activity in adolescent and adult patients with cystic fibrosis. *Rev Bras Ativ Fís Saúd* 2016; 21: 172–180.
38 Rasekaba TM, Button BM, Wilson JW, *et al.* Reduced physical activity associated with work and transport in adults with cystic fibrosis. *J Cyst Fibros* 2013; 12: 229–233.
39 Mackintosh KA, Ridgers ND, McNarry MA. Compensatory changes in physical activity and sedentary time in children and adolescents with cystic fibrosis. *J Sports Sci* 2019; 37: 1506–1511.
40 McNarry MA, Stevens D, Stone M, *et al.* Physical activity, sedentary time and sleep in cystic fibrosis youth: a bidirectional relationship? *Pediatr Pulmonol* 2021; 56: 450–456.
41 Valencia-Peris A, Lizandra J, Moya-Mata I, *et al.* Comparison of physical activity and sedentary behaviour between schoolchildren with cystic fibrosis and healthy controls: a gender analysis. *Int J Environ Res Public Health* 2021; 18: 5375.
42 Britto MT, Garrett JM, Konrad TR, *et al.* Comparison of physical activity in adolescents with cystic fibrosis *versus* age-matched controls. *Pediatr Pulmonol* 2000; 30: 86–91.
43 Jantzen A, Opoku-Pare M, Bieli C, *et al.* Perspective on cystic fibrosis and physical activity: Is there a difference compared to healthy individuals? *Pediatr Pulmonol* 2016; 51: 1020–1030.
44 Boucher GP, Lands LC, Hay JA, *et al.* Activity levels and the relationship to lung function and nutritional status in children with cystic fibrosis. *Am J Phys Med Rehabil* 1997; 76: 311–315.
45 Wells GD, Wilkes DL, Schneiderman-Walker J, *et al.* Reliability and validity of the habitual activity estimation scale (HAES) in patients with cystic fibrosis. *Pediatr Pulmonol* 2008; 43: 345–353.
46 Cox NS, Alison JA, Button BM, *et al.* Physical activity participation by adults with cystic fibrosis: An observational study. *Respirology* 2016; 21: 511–518.
47 Ward N, White D, Rowe H, *et al.* Physical activity levels of patients with cystic fibrosis hospitalised with an acute respiratory exacerbation. *Respir Med* 2013; 107: 1014–1020.
48 Baker CF, Wideman L. Attitudes toward physical activity in adolescents with cystic fibrosis: sex differences after training: a pilot study. *J Pediatr Nurs* 2006; 21: 197–210.

49 Hebestreit H, Schmid K, Kieser S, *et al.* Quality of life is associated with physical activity and fitness in cystic fibrosis. *BMC Pulm Med* 2014; 14: 26.
50 Tejero S, Cejudo P, Quintana-Gallego E, *et al.* The role of daily physical activity and nutritional status on bone turnover in cystic fibrosis: a cross-sectional study. *Braz J Phys Ther* 2016; 20: 206–212.
51 Schneiderman-Walker J, Wilkes DL, Strug L, *et al.* Sex differences in habitual physical activity and lung function decline in children with cystic fibrosis. *J Pediatr* 2005; 147: 321–326.
52 Quon BS, Patrick DL, Edwards TC, *et al.* Feasibility of using pedometers to measure daily step counts in cystic fibrosis and an assessment of its responsiveness to changes in health state. *J Cyst Fibros* 2012; 11: 216–222.
53 Schneiderman JE, Wilkes DL, Atenafu EG, *et al.* Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *Eur Respir J* 2014; 43: 817–823.
54 Ruf KC, Fehn S, Bachmann M, *et al.* Validation of activity questionnaires in patients with cystic fibrosis by accelerometry and cycle ergometry. *BMC Med Res Methodol* 2012; 12: 43.
55 Burtin C, Van Remoortel H, Vrijsen B, *et al.* Impact of exacerbations of cystic fibrosis on muscle strength. *Respir Res* 2013; 14: 46.
56 Burton KB, Morris NR, Reid D, *et al.* Increased physical activity post-exacerbation is associated with decreased systemic inflammation in cystic fibrosis – an observational study. *Physiother Theory Pract* 2020; 36: 1457–1465.
57 Elce A, Nigro E, Gelzo M, *et al.* Supervised physical exercise improves clinical, anthropometric and biochemical parameters in adult cystic fibrosis patients: a 2-year evaluation. *Clin Respir J* 2018; 12: 2228–2234.
58 Wieboldt J, Atallah L, Kelly JL, *et al.* Effect of acute exacerbations on skeletal muscle strength and physical activity in cystic fibrosis. *J Cyst Fibros* 2012; 11: 209–215.
59 Paranjape SM, Barnes LA, Carson KA, *et al.* Exercise improves lung function and habitual activity in children with cystic fibrosis. *J Cyst Fibros* 2012; 11: 18–23.
60 Groeneveld IF, Sosa ES, Pérez M, *et al.* Health-related quality of life of Spanish children with cystic fibrosis. *Qual Life Res* 2012; 21: 1837–1845.
61 Cherobin IA, Dalcin PTR, Ziegler B. Association between lung function, physical activity level and postural evaluation variables in adult patients with cystic fibrosis. *Clin Respir J* 2018; 12: 1510–1517.
62 Savi D, Simmonds N, Di Paolo M, *et al.* Relationship between pulmonary exacerbations and daily physical activity in adults with cystic fibrosis. *BMC Pulm Med* 2015; 15: 151.
63 Loutzenhiser JK, Clark R. Physical activity and exercise in children with cystic fibrosis. *J Pediatr Nurs* 1993; 8: 112–119.
64 Savi D, Di Paolo M, Simmonds NJ, *et al.* Is daily physical activity affected by dynamic hyperinflation in adults with cystic fibrosis? *BMC Pulm Med* 2018; 18: 60.
65 Hebestreit H, Kieser S, Rüdiger S, *et al.* Physical activity is independently related to aerobic capacity in cystic fibrosis. *Eur Respir J* 2006; 28: 734–739.
66 Tejero García S, Giráldez Sánchez MA, Cejudo P, *et al.* Bone health, daily physical activity, and exercise tolerance in patients with cystic fibrosis. *Chest* 2011; 140: 475–481.
67 Bhudhikanok GS, Wang MC, Marcus R, *et al.* Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study. *J Pediatr* 1998; 133: 18–27.
68 Van Remoortel H, Hornikx M, Demeyer H, *et al.* Daily physical activity in subjects with newly diagnosed COPD. *Thorax* 2013; 68: 962–963.
69 Chia M. Physical inactivity among children and adolescents in Singapore: a paradoxical issue. *Acta Kinesiologica* 2008; 2: 7–15.
70 Williams DP, Going SB, Lohman TG, *et al.* Body fatness and risk for elevated blood pressure, total cholesterol, and serum lipoprotein ratios in children and adolescents. *Am J Public Health* 1992; 82: 358–363.
71 Hanna RM, Weiner DJ. Overweight and obesity in patients with cystic fibrosis: a centerbased analysis. *Pediatr Pulmonol* 2015; 50: 35–41.
72 Barry PJ, Mall MA, Álvarez A, *et al.* Triple therapy for cystic fibrosis Phe508del–gating and –residual function genotypes. *N Engl J Med* 2021; 385: 815–825.
73 Caterini JE, Ratjen F, Barker AR, *et al.* Exercise intolerance in cystic fibrosis-the role of CFTR modulator therapies. *J Cyst Fibros* 2021; 21: 282–292.
74 Bell SC, Mall MA, Gutierrez H, *et al.* The future of cystic fibrosis care: a global perspective. *Lancet Respir Med* 2020; 8: 65–124.
75 Trudeau F, Laurencelle L, Shephard RJ. Tracking of physical activity from childhood to adulthood. *Med Sci Sports Exerc* 2004; 36: 1937–1943.
76 Telama R, Yang X, Leskinen E, *et al.* Tracking of physical activity from early childhood through youth into adulthood. *Med Sci Sports Exerc* 2014; 46: 955–962.
77 Telama R, Yang X, Viikari J, *et al.* Physical activity from childhood to adulthood: a 21-year tracking study. *Am J Prev Med* 2005; 28: 267–273.

78 Uchmanowicz I, Jankowska-Polańska B, Rosińczuk J, *et al.* Health-related quality of life of patients suffering from cystic fibrosis. *Adv Clin Exp Med* 2015; 24: 147–152.

79 Corder K, Sharp SJ, Atkin AJ, *et al.* Change in objectively measured physical activity during the transition to adolescence. *Br J Sports Med* 2015; 49: 730–736.

80 Kallio J, Hakonen H, Syväoja H, *et al.* Changes in physical activity and sedentary time during adolescence: gender differences during weekdays and weekend days. *Scand J Med Sci Sports* 2020; 30: 1265–1275.

81 Shin KC. Physical activity in chronic obstructive pulmonary disease: clinical impact and risk factors. *Korean J Intern Med* 2018; 33: 75–77.

82 Cerny FJ, Pullano TP, Cropp GJ. Cardiorespiratory adaptations to exercise in cystic fibrosis. *Am Rev Respir Dis* 1982; 126: 217–220.

83 Killian KJ, Jones NL. The use of exercise testing and other methods in the investigation of dyspnea. *Clin Chest Med* 1984; 5: 99–108.

84 Jarad NA, Giles K. Risk factors for increased need for intravenous antibiotics for pulmonary exacerbations in adult patients with cystic fibrosis. *Chron Respir Dis* 2008; 5: 29–33.

85 Arikan H, Yatar İ, Calik-Kutukcu E, *et al.* A comparison of respiratory and peripheral muscle strength, functional exercise capacity, activities of daily living and physical fitness in patients with cystic fibrosis and healthy subjects. *Res Dev Disabil* 2015; 45–46: 147–156.

86 Barry SC, Gallagher CG. Corticosteroids and skeletal muscle function in cystic fibrosis. *J Appl Physiol* 2003; 95: 1379–1384.

87 Orenstein DM, Franklin BA, Doershuk CF, *et al.* Exercise conditioning and cardiopulmonary fitness in cystic fibrosis. The effects of a three-month supervised running program. *Chest* 1981; 80: 392–398.

88 Klijn PH, Oudshoorn A, van der Ent CK, *et al.* Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest* 2004; 125: 1299–1305.

89 Matthews CE, Moore SC, George SM, *et al.* Improving self-reports of active and sedentary behaviors in large epidemiologic studies. *Exerc Sport Sci Rev* 2012; 40: 118–126.

90 Reilly JJ, Penpraze V, Hislop J, *et al.* Objective measurement of physical activity and sedentary behaviour: review with new data. *Arch Dis Child* 2008; 93: 614–619.

91 Rabinovich RA, Louvaris Z, Raste Y, *et al.* Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J* 2013; 42: 1205–1215.

92 Demeyer H, Mohan D, Burtin C, *et al.* Objectively measured physical activity in patients with COPD: recommendations from an international task force on physical activity. *Chronic Obstr Pulm Dis* 2021; 8: 528–550.

93 Trost SG, Pate RR, Freedson PS, *et al.* Using objective physical activity measures with youth: how many days of monitoring are needed? *Med Sci Sports Exerc* 2000; 32: 426–431.

94 Gába A, Dygrýn J, Mitáš J, *et al.* Effect of accelerometer cut-off points on the recommended level of physical activity for obesity prevention in children. *PLoS One* 2016; 11: e0164282.