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Review

Physical fitness levels and moderators in people with epilepsy: A systematic review and meta-analysis

Davy Vancampfort [a,b,*], Philip B. Ward [c,d], Brendon Stubbs [e,f]

[a] KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium
[b] KU Leuven – University of Leuven, University Psychiatric Center KU Leuven, Leuven-Kortenberg, Belgium
[c] School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
[d] Schizophrenia Research Unit, Ingham Institute of Applied Medical Research, Liverpool, NSW, Australia
[e] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK
[f] Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, UK

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ABSTRACT

Cardiorespiratory fitness (CRF) is a modifiable risk factor for mental and physical chronic conditions and premature mortality. Cardiorespiratory fitness levels and moderators among people living with epilepsy are unknown. The aim of the current meta-analysis was to (1) determine mean CRF in people living with epilepsy and compare levels with age- and gender-matched healthy controls (HCs), and (2) explore moderators of CRF. Major electronic databases were searched systematically for articles reporting CRF expressed as maximum or peak oxygen uptake (ml/min/kg). A random effects meta-analysis calculating the pooled mean CRF including subgroup- and meta-regression analyses was undertaken. Across 4 studies, the CRF level was 31.4 ml/kg/min (95% confidence interval [CI] = 27.3 to 35.5) (n = 121; mean age = 29–43 years). Compared with age- and gender-matched controls (n = 39), in people with epilepsy (n = 39), CRF levels were 4.9 ml/kg/min (95%CI = −5.9 to −3.9) lower (P < 0.001). Cardiorespiratory fitness levels obtained via maximal tests were significantly (P < 0.001) lower than obtained via submaximal tests. Future research should explore underlying mechanisms for the observed impairment in CRF in people with epilepsy.

1. Introduction

People living with epilepsy die prematurely compared with people from the general population [1]. Recently, it has become clear that part of this premature mortality might be attributable to a higher cardiovascular disease (CVD) risk [2]. Current hypotheses link the increased incidence of these cardiovascular comorbidities to (a) altered autonomic function, (b) accelerated fibrosis and myofibrillar degeneration due to repeated hypoxemia, (c) cardiotoxic effects of excess catecholamines during and following seizures, and/or (d) adverse effects of antiepileptic drugs [3]. In the general population, there is robust evidence demonstrating that low cardiorespiratory fitness (CRF, the ability of the circulatory and respiratory systems to supply oxygen to working muscles during sustained physical activity) is a strong predictor for CVDs [relative risk (RR) = 1.56; 95% confidence interval (CI) = 1.39–1.75; P < 0.001] and all-cause mortality (RR = 1.70; 95%CI = 1.51–1.92; P < 0.001) [4]. Improving CRF via physical activity is a key component of preventing and treating CVD and reducing associated mortality [5]. People with epilepsy are known to be less physically active than age- and gender-matched controls [6–10]. While in the past, patients were often advised against participating in physical activity, mostly because of fear, overprotection, and ignorance, there is now a strong consensus that all people living with epilepsy, irrespective of their age, should be advised to augment their physical activity levels [11]. It remains, however, unclear whether people with epilepsy have lower CRF levels than matched controls from the general population. It is also unclear whether treatment-related (e.g., antiepileptic exposure) and clinical variables (e.g., epilepsy subtype) moderate CRF levels in this population. Pooled analyses exploring subgroup differences in CRF among people with epilepsy are highly relevant as they enable risk stratification. Pooling data also allows for more thorough investigation of the effect of assessment variables (e.g., maximal versus submaximal and running versus cycling) on CRF levels. In order to address the current gaps in the literature, we conducted a meta-analysis with the following aims: (a) investigate the mean pooled CRF level in people with

* Corresponding author at: Leuvensesteenweg 517, B-3070 Kortenberg, Belgium.
E-mail address: Davy.Vancampfort@uc-kortenberg.be (D. Vancampfort).

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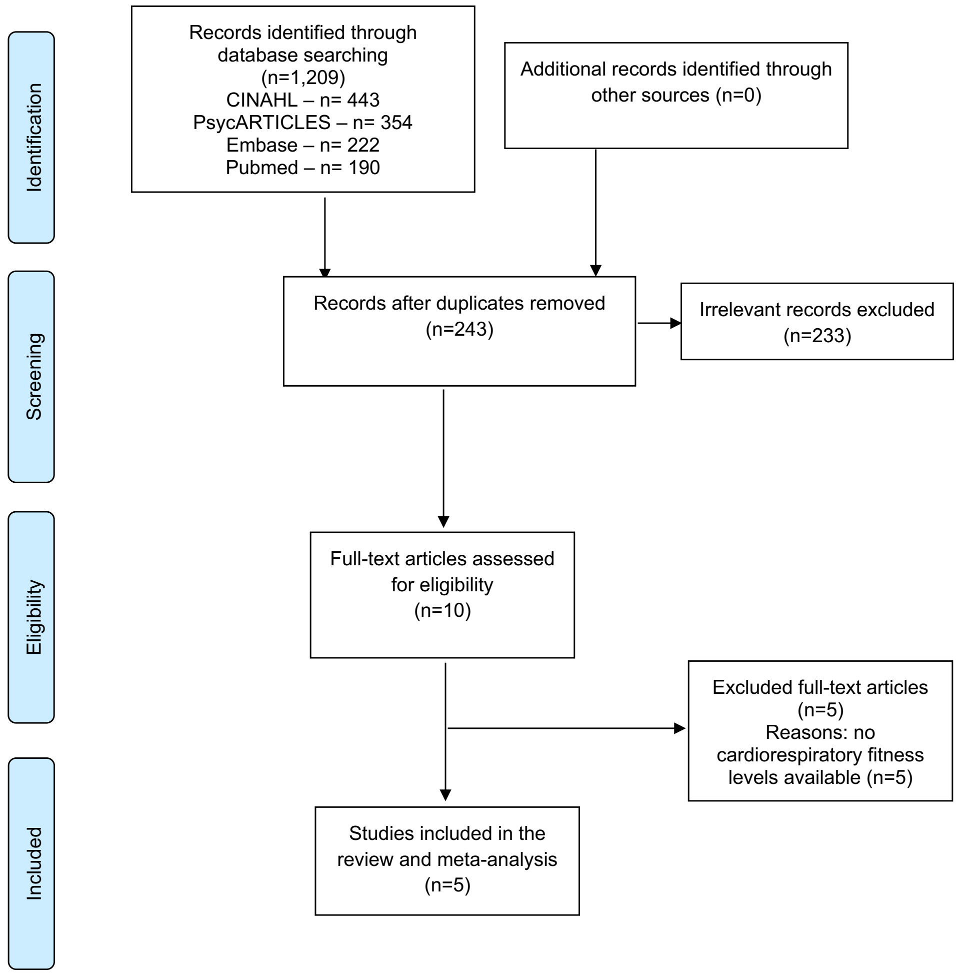

Fig. 1. Flow diagram.

epilepsy and compare CRF levels where possible with age- and gender-matched healthy controls, and (b) explore moderators of CRF levels in people living with epilepsy.

2. Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. Two researchers searched PubMed, Embase, PsycARTICLES, and CINAHL from database inception to 01/03/2019. Keywords used were “cardiorespiratory” or “aerobic” and “epilepsy” in the title, abstract, or index term fields. Manual searches were also conducted using the reference lists from recovered articles. Inclusion criteria were as follows: (1) inclusion of adult participants with a diagnosis of epilepsy and (2) measurement of CRF (mean $\pm$ standard deviation) expressed as maximal oxygen uptake, VO_2 max, or VO_2 peak (ml/kg/min) and assessed with a maximal exercise test or estimated with a submaximal exercise test. No additional exclusion criteria were applied. After the removal of duplicates, two reviewers screened titles and abstracts of all potentially eligible articles. Both authors applied eligibility criteria, and a list of full-text articles was reached through consensus. In case of study overlap, the most recent study was included. Data extracted for exploring moderators of CRF included assessment variables (maximal versus submaximal and running versus cycling), participants' characteristics including mean age (years), % male, mean body mass index, and clinical variables including mean illness duration (years), and type of epilepsy. If age- and gender-matched healthy control data were available, in addition to the primary outcome, age and % male in the healthy control groups were extracted. Random effects meta-analyses were conducted using Comprehensive Meta-Analysis software (Version 3, Biostat, Englewood, New Jersey). First, we pooled the mean CRF level among people with epilepsy and where possible compared this to healthy controls. Second, we compared baseline CRF levels between assessment variables (maximal versus submaximal and running versus cycling) and type of epilepsy (temporal lobe versus other epilepsy). Statistical heterogeneity was assessed using the I^2 statistic. Publication bias was assessed with the Begg and Mazumdar test [13]. For all analyses, we calculated the trim and fill adjusted analysis [14] to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size.

3. Results

3.1. Search results

A total of 243 unique records were identified. After screening titles and application of the eligibility criteria, five studies including six analyses were eligible for inclusion in the meta-analysis. Fig. 1 presents the flow of studies through the review process.

3.2. Characteristics of included studies

There were four cross-sectional studies [7,15–17] including five CRF values and one intervention study [18]. Participants in the intervention

Table 1
Characteristics of the included studies.

Author	VO_2 peak/max	Design	Assessment method	Cycling/running	Sample size	Age	% male	Type epilepsy
Volpato [7]	27.5 ± 4.6	1	1	1	38	43.0	0.37	1
Vancini [15]	28.8 ± 6.7	1	1	2	20	34.1	0.45	1
Vancini [16]	28.5 ± 1.6	1	1	2	19	35.6	0.42	1
Bjorholt [17] (men)	38	1	2	2	21	29.3	1	2
Bjorholt [17] (women)	34	1	2	2	23	29.3	0	2
Nakken [18][a]	32.3	2	2	2	21	29	0.48	2

VO_2 peak/max = peak/maximal oxygen uptake expressed as ml/min/kg (mean ± standard deviation); assessment method: 1 = a maximal exercise test, 2 = a submaximal exercise test; cycling/running: 1 = exercise test on a treadmill, 2 = exercise test on a cycle ergometer; design: 1 = cross-sectional study, 2 = one-arm pretest posttest study; type of epilepsy: 1 = temporal lobe epilepsy, 2 = mixed subtypes.

[a] Overlap with Bjorholt [17]: this study is only included in the narrative review and not in the meta-analysis.

study of Nakken and colleagues [18] overlapped with the cross-sectional study of Bjorholt and colleagues [17] and were, therefore, excluded from the meta-analysis. Across the four cross-sectional studies, the final dataset included 121 people with epilepsy. Three CRF values were assessed with maximal and two with submaximal exercise tests. Four CRF values were assessed on a cycle ergometer and one on a treadmill. Among available studies, the mean age ranged from 29 to 43 years, the percentage of male participants from 37% to 47%. Three studies focused on patients with temporal lobe epilepsy while one study was in patients with different epileptic subtypes. Details for all studies are provided in Table 1.

In the study of Nakken et al. [18], CRF improved significantly from an average value of 32.3 ml/kg/min to 39.6 ml/kg/min following four weeks of aerobic exercise, three times per week for 45 min at moderate intensity, i.e., 60% of the VO_2 max.

3.3. Cardiorespiratory fitness in people living with epilepsy

Across the four studies (including five CRF values), the pooled mean predicted VO_2 max or VO_2 peak was 31.4 ml/kg/min (95%CI = 27.3 to 35.5; $I^2 = 98.1\%$; Kendall's tau = 0.20, P = 0.31; Egger = 4.6, P = 0.32).

3.4. Cardiorespiratory fitness in people living with epilepsy versus matched controls

Two studies [15,16] compared the CRF levels of people with epilepsy (n = 39) with age- and gender-matched controls (n = 39). The mean difference was −4.9 ml/kg/min (95%CI = −5.9 to −3.9) (P < 0.001; $I^2 = 0$).

3.5. Moderators of cardiorespiratory fitness in people living with epilepsy

Full details of the subgroup analyses of CRF levels are summarized in Table 2. Lower CRF levels were found in maximal versus submaximal exercise tests (P < 0.001). There was a trend for higher CRF values in cycle ergometer versus treadmill tests (P = 0.06). Studies in people with temporal lobe epilepsy showed a higher CRF than CRF values in studies with mixed subtypes (P < 0.001).

4. Discussion

This is the first meta-analysis investigating mean CRF levels in people with epilepsy. The trim and fill adjusted pooled mean CRF was 31.4 ml/kg/min (95%CI = 27.3 to 35.5) (N studies = 4; n participants = 121). The current study demonstrates that people with epilepsy have on average, a 4.9 ml/kg/min (95%CI = −5.9 to −3.9) lower VO_2 max than age- and gender-matched controls from the general population. This finding should, however, be considered with caution as it was based on two studies (39 people with epilepsy and 39 controls). However, this difference is clinically relevant as in the general population, every 3.5 ml/kg/min reduction in VO_2 peak is associated with 13% and 15% increases in risk of all-cause mortality and CVD, respectively [4]. Also of clinical relevance is that CRF levels can improve significantly (+7.3 ml/kg/min) after 4 weeks of aerobic exercise, three times per week for 45 min at moderate intensity, very likely also reducing the CVD morbidity risk [18]. Our meta-analysis is also the first to demonstrate that maximal testing protocols predicted lower CRF levels than submaximal protocols. Future research should explore underlying mechanisms for these differences. Although exhaustive exercise is not a seizure-inducing factor [16], it cannot be excluded that some people with epilepsy stopped their maximal exercise test prematurely, i.e., before their maximal threshold had been reached. Therefore, future research should explore whether lower CRF in people with epilepsy observed in this meta-analysis is associated with the avoidance of potentially anxiogenic activities. However, when looking more in detail at the people with epilepsy who were tested in the different studies, we found that in the studies using maximal tests, only patients with temporal epilepsy were included while in the studies using submaximal test, people with a wide range of epilepsy subtypes were tested. To date, the CRF levels between people with different subtypes of epilepsy have not been investigated. While the results are novel, some caution should be attached to these findings because of small number of studies included in some subanalyses and limitations in reporting of other

Table 2
Subgroup analyses of cardiorespiratory fitness (expressed as ml/min/kg) in people living with epilepsy.

Analysis	N studies	N participants	Meta-analysis			I^2	P
			Point estimate	95%CI			
• Maximal versus submaximal testing						98.0	0.001*
- Maximal	3	77	28.3	27.7	29.0		
- Submaximal	2	44	36.0	35.0	36.7		
• Treadmill versus cycle ergometer test						98.4	0.06
- Treadmill	1	38	27.5	26.0	29.0		
- Cycle ergometer	4	83	32.4	27.5	37.3		

* Significant when P < 0.05.

important variables such as specific antiepileptic treatments, type of epilepsy, and relevant lifestyle factors (physical activity, smoking).

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Declaration of Competing Interest

None.

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