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Systematic Review or Meta-analysis

Is there an association between cardiorespiratory fitness and stage of illness in psychotic disorders? A systematic review and meta-analysis

Heggelund J, Vancampfort D, Tacchi MJ, Morken G, Scott J. Is there an association between cardiorespiratory fitness and stage of illness in psychotic disorders? A systematic review and meta-analysis.

Background: Clinical staging models describe where an individual exists on a continuum from asymptomatic at-risk states (Stage 0) through to established late-stage disease (Stage 4). We applied this framework to systematically assess evidence for any associations between objectively assessed cardiorespiratory fitness (CRF) and stage of psychosis.
Method: Nine electronic databases were searched for relevant publications from inception until October 31, 2019. Pooled effect sizes (Hedges' *g* and 95% confidence intervals (95% CI)) were estimated for differences in CRF for studies that reported mean oxygen uptake (max, peak, or predicted VO_2 in ml/kg/min).

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Summations

- This systematic review and meta-analysis is the first to compare objectively assessed cardiorespiratory fitness (CRF) across each clinical stage of psychosis (i.e., Stages 0–4) with general population or HC groups. It demonstrates that CRF is reduced across the entire spectrum of psychosis, including in many at-risk populations, and shows that the decrease in CRF identified in late-stage psychosis means that many patients have an aerobic capacity below that required for functional daily living.
- There is an incremental decrease in mean CRF from healthy controls to Stage 4 cases, with moderate to large effect sizes between each clinical stage. The reduction in CRF was statistically significant between healthy controls and Stage 1 (subthreshold medication-naïve presentations) and between Stage 2 (first episode) and Stage 3 (established illness).
- The 28% decrease in CRF between Stage 1 and Stage 4 psychosis (mean decrease in VO_2 ~10 ml/kg/min) is clinically important as every 3.5 ml/kg/min decrease in VO_2 is associated with a 13% and 15% increase in the risk of all-cause premature mortality and cardiovascular disease-associated premature mortality respectively.

Limitations

- Many publications of objective assessment of CRF and psychosis do not specifically refer to stage of illness and so it is possible our search criteria failed to identify some eligible studies.
- We could not include any data for Stage 0 samples in the meta-analyses, and the only eligible Stage 1 sample was very small, which calls into question the representativeness of that data.
- The cross-sectional nature of most studies and the hypotheses for this review mean that we cannot comment on direct causality (between stage and CRF). Also, insufficient data were available to examine confounding of medications, coexisting physical disorders or nicotine consumption.

Results: Thirty-eight studies were eligible. Findings indicated that suboptimal CRF can be present at Stages 0 and 1. Meta-analyses of 22 studies demonstrated that CRF was significantly reduced in individuals classified between Stages 1 and 4 compared with matched or general population controls ($g = -0.93$; 95% CI −1.14, −0.71). Mean VO_2 was decreased by 28% in Stage 4 compared with Stage 1 (34.1 vs. 24.66 ml/kg/min); the largest effect size for CRF reduction was reported between Stages 2 and 3 ($g = -1.16$; 95% CI −1.31, −1.03).
Conclusions: Although not identifying direct causal links between clinical stage and CRF, using this framework may enhance understanding of co-associations between mental and physical health markers across the entire spectrum of psychosis. Limitations include lack of research on CRF in Stages 0 and 1 alongside problems determining stage in some studies. However, impaired CRF is reported in emerging psychosis, supporting calls that early intervention programmes should address both mental and physical wellbeing.

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Key words: clinical staging; psychosis; cardiorespiratory fitness; meta-analysis

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Introduction

Clinical staging models are routinely employed to enhance the systematic management of physical disease processes such as cancer and cardiovascular disease (CVD). Clinical staging models categorize key features related to illness trajectory within putative stages. Importantly, the model extends beyond the notion of severity and duration of illness to try to capture disease progression and extension across a range of parameters (as clearly represented by the tumor, node, metastases classification and its multiple subcategories). It is increasingly recognized that there are clinical and research benefits of applying staging models in psychiatry, and many investigators have published ideas about the clinic–pathological boundaries between different stages of psychotic disorders (1). Most staging frameworks describe where an individual exists on a continuum from an asymptomatic (but biological at risk) state through clinical high-risk (CHR) or ultra-high-risk (UHR) presentations, early-stage disease (e.g., the first-episode meeting diagnostic criteria) and finally to established illness, referred to as end or late-stage disease (2). This research is ongoing, and there are several unresolved challenges. For example, it is acknowledged that staging is more nuanced than simply a combination of severity of illness, but in psychiatry, it is hard to capture all the core elements of disease progression, and current research is attempting to go beyond the over-reliance on proxies related to illness duration and severity of core symptoms of a diagnosis, to incorporate, for example, levels of disability, neurocognitive impairment, and possibly links with or extension to other pathophysiological or bodily systems.

To date, psychiatry research has primarily focused on stage-specific psychopathology and the optimal interventions that can be offered to individuals presenting with illness at different clinical stages with a smaller number of studies exploring the neuropsychological or functional deficits associated with each putative illness stage (3). There is currently a debate in psychiatry about the benefits of and evidence to support the use of diagnosis-specific or trans-diagnostic staging models in day-to-day practice (2, 3). While the former models have many critics, diagnosis-specific models have been the subject of several large-scale studies and there is some consensus on the criteria that can be used to define specific clinical stages (see Appendix S1). No such consensus is currently lacking for trans-diagnostic staging models. Given the state of the art, we decided to focus the current study on a disorder-specific staging model, namely the framework currently applied to psychotic disorders (see Appendix S1 for details). We especially wanted to explore a critical component of medical staging models that has not been addressed by psychiatry research, namely the notion of disease extension. This concept is an established element of medical models; for example, the clinical staging of Hodgkin's disease considers spread by location (lymph nodes above and below the diaphragm) and bodily system (organs such as the spleen and liver). Although the concept of disease extension is underdeveloped in staging research in psychiatry, recent publications support the notion of multisystem disease in major mental disorders. We propose that insights into these emerging strands of research might be further illuminated by examining the evidence for any associations between putative clinical stages of a major mental disorder such as psychosis

and a selected marker of or presumed risk factor for major medical illnesses (4). However, it is important to emphasize the exploratory nature of this approach and that we do not presume to suggest that any associations represent direct causality between illness stage and physical health markers.

A recognized feature of all major mental disorders is the increased prevalence of physical morbidity such as cardiorespiratory diseases and associated premature mortality compared with the general population (5). For example, large-scale studies and meta-analyses have highlighted that a known risk factor for cardiovascular disease, namely cardiorespiratory fitness (CRF), is reduced in individuals with established psychotic disorders (6). This is important as research indicates that physical fitness is a mediator of the effects of physical activity on health outcomes and any decrease in CRF may represent a complex interplay between genetic, environmental, social, illness, and treatment-related factors (7). Indeed, the American Heart Association has published an official scientific statement advocating that CRF be categorized as a clinical vital sign that should be incorporated into routine clinical assessments. Interestingly, there is emerging evidence that impaired CRF may be present in those with first-episode psychosis (FEP), who probably have more limited exposure to adverse social or treatment-related consequences of prolonged illness, etc. (8). In addition, CRF may be a putative trans-diagnostic marker of disease extension in a range of mental disorders, as we recently demonstrated that lower CRF in young adults is associated with a higher incidence of new onsets of a number of adverse mental health outcomes (9).

Given the above, we examined evidence of any association between objectively assessed CRF and each clinical stage of psychotic disorders. Previous systematic reviews and meta-analyses focused on either middle-aged adults with established psychotic disorders or (less often) on FEP (7–10) without considering different clinical stages. As such, this review offers a template for exploring different physical markers in disorder-specific staging models and/or exploring the concept of disease extension by, for example, considering a specified marker of physical disorders to studies utilizing trans-diagnostic staging models.

Aims of study

The aim of the current systematic review and meta-analysis is to:

i examine objectively assessed cardiorespiratory fitness in individuals included in samples defined as being at clinical Stages 0–4 of psychotic disorders and compare the cardiorespiratory fitness findings with general population or healthy control groups and
ii estimate the magnitude of any differences in cardiorespiratory fitness between each different clinical stages (e.g., to determine whether there is any decline in cardiorespiratory fitness between Stages 1 and 2, 2 and 3, or 3 and 4).

Material and methods

The protocol was lodged with the international prospective register of systematic reviews in August 2017 (PROSPERO: CRD42017075709), and we adhered to the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. A PRISMA flowchart is provided in Figure 1, and a PRISMA checklist is provided in the supplementary materials (Appendix S2).

Search strategy

A systematic strategy was employed to search for relevant studies (see online Supplementary Appendix S3 for the details). Search terms referring to the objective assessment of CRF (e.g., cycle ergonomic test) and psychotic disorders or risk states (e.g., offspring, clinical high risk) were cross-referenced with terms identifying observational, cross-sectional, prospective, cohort studies and/or randomized controlled clinical trials (RCTs). Also, we incorporated selected search terms used in previous systematic reviews of physical fitness (7, 9).

Electronic databases (EBSCOhost, SPORTDiscus, Embase, MEDLINE, Cochrane database, Health Technology Assessment Database, CINAHL, PsycINFO, and Dissertation Abstracts) were searched from inception until October 31, 2019. Further, we investigated journals that publish articles on related themes (e.g., Early Intervention in Psychiatry), conference proceedings (e.g., SIRS) and citations listed in identified studies. We contacted four researchers of relevant studies to obtain additional data or information, to identify possible gray literature and/or to determine the relevance of other studies that had been completed but not yet published.

Selection criteria

There was no restriction on year of publication, and articles written in English, French, Spanish, Italian,

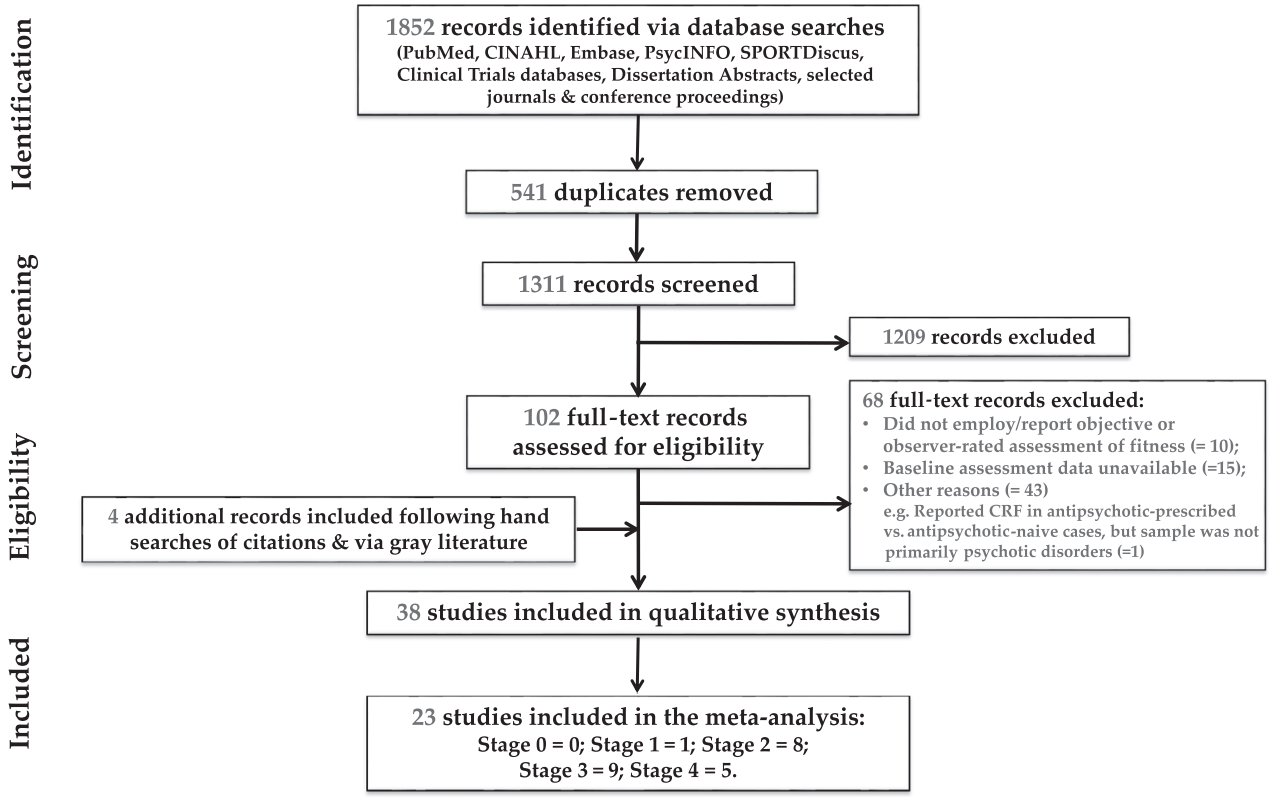


Fig. 1. PRISMA diagram of systematic search for identification and selection of studies.

Portuguese, Dutch, German, Norwegian and Scandinavian languages were eligible for screening.

Publications were included if they reported sample mean scores for recognized objectively assessed parameters of CRF (e.g., VO_2 max measured in ml/kg/min) (11) for subgroups that could be classified according to stage of illness or subgroups classified as healthy control (HC) (minimum subgroup size = 10). We used published frameworks (1, 2) to operationalize stage of illness and the online supplementary material (Appendix S3 provides the details for how each stage was defined and how samples including individuals meeting criteria for more than one stage were classified). For example, the minimum criteria for classification of a study as comprising of a Stage 1 sample were that the clinical presentation that met recognized, published criteria for ultra-high Risk or CHR that had been used in previous studies of clinical staging of psychosis (12). Stage 2 was operationalized as the first threshold episode meeting recognized diagnostic criteria (e.g., ICD or DSM) in a sample recruited from community, out- or in-patient settings, etc.

Studies where a subsample of the study population met the eligibility criteria were eligible for inclusion in the qualitative review. However, inclusion in the meta-analysis depended on availability of specific data for a subgroup identified and classified according to clinical stage criteria and data on mean VO_2 measures (maximum, predicted, or peak) being available for that subgroup. For RCTs, only baseline data were included in the meta-analysis; for prospective studies, only outcome data from the initial follow-up were eligible.

Publications that included the key search terms in the title, abstract, or index term fields were screened, and full-text articles were obtained as appropriate. Duplicate publications were removed, and uncertainties regarding eligibility were reconciled by consensus (JS and JH).

Data extraction

Data were extracted from studies meeting selection criteria, and the following key information was entered into a proforma (by JH; then checked by MJT and JS): study location, design and publication date; sample size, demographics, and any anthropometric details (e.g., body mass index (BMI) measured in kg/m^2); technique for measuring CRF and data on reported parameters (e.g., raw scores of VO_2

parameters or proportion of individuals with high, medium, or low CRF); equivalent information for any comparison groups; and classification of each study regarding clinical stage of the index group. Insufficient data were available in eligible studies regarding exposure to psychotropics, nicotine consumption, or other cardiorespiratory risk factors (so we abandoned attempts to include these in the summary tables). We recorded data on statistical measures of association (e.g., odds ratios), the magnitude of any associations, and whether the analyses were adjusted for or reported any potential confounders, etc. If summary statistics were not reported, we estimated these from the reported findings if possible or requested raw data from the original authors.

Key information from the proforma is summarized in Tables 1 and 2, but, to enhance readability of tables, we excluded some of the data on the proforma (these details are available from the authors on request).

Quality assessment

Quality of included studies was assessed independently by three raters (MJT, JH, and GM) using the 14-item Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (available at http://nhlbi.nih.gov). Assessors reviewed each publication, and differences in ratings (total score out of 14 and a quality grading of good, fair, or poor) were resolved by consensus. The jointly agreed score and grading was recorded for each study.

Synthesis and statistical analysis

A qualitative review was undertaken to summarize findings from all eligible studies. Those studies that measured CRF objectively using VO_2 (max, peak or predicted VO_2) that provided data for samples meeting criteria for one specific clinical stage (for details, see above and Appendix S1) were eligible for inclusion in the meta-analysis. For the pooled analyses, data were entered into an electronic database and analyzed using the Comprehensive Meta-Analysis software package (version 3).

Pooled effect sizes (ES) for objectively measured CRF and clinical stage were calculated as Hedges' g and 95% confidence intervals (95% CIs). Reported ES are based on random-effects models in order to account for heterogeneity between studies. We considered an ES of <0.5 as small and >0.8 as large. Heterogeneity was evaluated using the Q statistic, and its magnitude was measured using the I^2 index. An $I^2 \geq 50\%$ (with chi-squared, $P < 0.05$) was regarded as indicative of moderate degree of heterogeneity and ≥75% as a high degree.

The first meta-analysis focused on studies where individuals at risk of or with a diagnosis of a psychotic disorder were compared with non-cases (HC, general population groups, etc.). The ES are reported for each clinical stage (Stage 1, 2, 3, or 4) vs. the comparator group and the overall ES (all stages combined vs. all control groups combined). In addition to reporting Hedges' g, we employed meta-regression to explore any confounding associated with age or sex distribution (proportion of males) and BMI. We used funnel plots and Egger's regression method to explore the risk of publication bias. In addition, the fail–safe number was calculated to determine the number of unpublished null studies, which would be required to invalidate our findings ($P > 0.05$).

In the second meta-analysis, we estimated the ES for CRF pairwise across HC and Stage 1, then across clinical stages (Stage 1 vs. 2; Stage 2 vs. 3, etc). These analyses allowed inclusion of some cross-sectional studies that lacked comparison groups. In the main text, we provide a diagrammatic representation of the findings regarding change in mean VO_2, with the classic forest plot included in the online supplementary material (Appendix S4).

We planned sensitivity analyses (subject to number of eligible studies available) to assess whether effects were still observed following the removal of publications using less reliable CRF tests or parameters (e.g., excluding studies using the 6-min walk test), involving broader case mixes (e.g., affective and non-affective psychoses) or with methodologies rated as poor quality, etc. Lastly, we considered whether the ES varied according to the degree of certainty of assessors (MJT and JS) in the accuracy of the clinical stage classification of each sample.

Results

The PRISMA flowchart is shown in Figure 1, and the characteristics of included studies are summarized in Tables 1 and 2.

Description of included studies and quality assessment

As shown in Tables 1 and 2, 38 studies met criteria for inclusion in the qualitative synthesis and all were published after 2005 (8, 13–49).

Twenty studies were undertaken in Europe (of which nine were from Scandinavia), 10 in North America, five in Asia, and three in Australia. Sample sizes varied largely in relation to the type of study; for instance, the cohorts included between 2682 and 1.1 million participants and were >80%

Table 1. Eligible studies that include cases classified as Stage 0, 1 or 2

Study (1st author; year of publication; location; reference number)	Design	Cases†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Stages 0, 1, & 2: mixed sample studies						
Koivukangas [2010], Finland (13)	North Finland 1986 birth-cohort	Follow-up of 6987 adolescents; 48% males; Aged 15–16 years Three psychosis risk groups: family history of psychosis (n = 122), high number of prodromal symptoms (n = 401) or developed a FEP syndrome (n = 33).	Cycle ergometer test	VO_2 peak (reported as terciles) Low CRF rates at baseline differed for incident psychosis vs. no psychosis (46% vs. 33%), but differences were non-significant for familial risk or number of prodromal symptoms		
Lederman [2017], Australia (14)	Cross-sectional 3-group study	30 individuals (23 males): 10 out-patients at risk of psychosis (met criteria for ARMS) & 10 FEP. age 21.0 ± 1.1; BMI 23.8 ± 4.1	Cycle ergometer test.	VO_2 max: ARMS = 34.1 ± 9.4; FEP = 32.9 ± 13.8	10 HC with similar age & sex profiles Mean BMI in HC (22.2) non-significantly lower than ARMS (24.0) & FEP (25.1)	VO_2 max = 42.0 ± 9.8

Stage 2: cohort studies	Design	Cohort participants†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Gubata [2013], USA (15)	Prospective cohort study of US army trainees (recruited 2005–2006)	Total sample = 11 369 (~80% males); 10 216 = weight qualified participants (WQP); age ≥18 years (>80% were 18–24); BMI 18.5–24.9 = ~50%	5-minute step test	At one-year follow-up, 37 new onsets of psychosis occurred in WQP; the OR for psychosis in WQP who failed the fitness test was 1.3 (0.64–2.63)		
Kunutsor [2017], Finland (16)	Finnish Kuopio IHD longitudinal follow-up study	2682 males aged 42–61 years (mean ~53 ± 5)	Respiratory gas exchange analysis; cycle ergometer test	VO_2 max at baseline assessment = 30.4 ± 8.0FEP = 215HR for psychosis per SD increase in baseline CRF = 0.79 (0.67–0.92).		
Nyberg [2017], Sweden (17)	Prospective population-based cohort study (recruited between 1968 and 2005)	>1.1 million Swedish conscripts (all males) with no history of mental disorders; Enlistment (& CRF testing) at 18 yearsBMI 21.8 ± 3.2	Cycle ergometer test with heart rate measured constantly; fitness categorized as low, medium, and high	In the low CRF group, the HR was 1.44 (1.26–1.61) for onset of schizophrenia spectrum disorders and 1.41 (1.27–1.56) for onset of other psychoses		

Stage 2: single group or case–control studies	Design	Cases†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Lin [2011], Hong Kong (18)	Cross-sectional (3-arm RCT)	140 females with onset of DSM-IV psychosis within ~2 years (~10% = affective psychoses); age 24.5 ± 7.5 years	Treadmill walking test with HR monitoring for randomized cases (n = 96)	VO_2 max = sample mean: 26.2 ± 5.6		
Gretchen-Doorly [2012], USA (19)	Cross-sectional	70 cases with onset of psychosis within 2 years; age 21.8 ± 3.7 years; BMI 28.2 ± 5.6	YMCA fitness test: protocol assessed CRF via a 3-min step test	Raw scores converted to age- and sex-based percentile ranks CRF mean percentile score = 40.3 ± 13.3		
Abdel-Baki [2013], Canada (20)	Cross-sectional (case series)	25 male in-patients with DSM-IV psychosis (n = 18) or bipolar disorder (n = 7); age 24.8 ± 3.7 years; BMI 32.1 ± 3.7	Treadmill walking test undertaken at baseline in study completers (n = 16) and non-completers (n = 9)	VO_2 max = Sample mean: 36.5 ± 12.7		

Table 1. (Continued)

Stage 2: single group or case–control studies	Design	Cases†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Nyboe [2015]‡, Denmark (8)	Longitudinal follow-up study	99 (66 males) out-patients with ICD-10 psychosis; age 24.9 ± 7.1 years; BMI 24.9 ± 4.3	Cycle ergometer test with HR monitoring	VO_2 max = 36.9 ± 12.9	50 matched HC	VO_2 max = 53.3 ± 13.2
Rosenbaum [2015], Australia (21)	Cross-sectional (case series)	19 (10 males) in-patients with <3 years of DSM-IV psychosis; age 19.9 ± 2.4 years	Cycle ergometer test.	VO_2 max predicted = 32.8 ± 7.1; 11 cases (61%) <20th percentile for norms		
Curtis [2016], Australia (22)	Cross-sectional (non-randomized 2-group comparison)	28 (17 males) out-patients with DSM-IV psychosis (mood disorders = 6); age 20.7 ± 2.2 years (range 17–25); BMI 18.5–24.9 = 61%.	Assessed in intervention group onlyNo details of specific CRF test employed	VO_2 max = Intervention group (n = 16; males = 7) =30.6 ± 6.5		
Vancampfort [2017], Belgium (23)	Cross-sectional	29 (21 males) of 33 consecutive out-patients with DSM-V first-episode psychosis; age 22.8 ± 5.1 years, BMI 24.2 ± 3.4	Cycle ergometer test with HR monitoring	VO_2 max: males = 33.4 ± 8.4; females = 25.1 ± 4.0		

ARMS, at-risk mental state; BMI, body mass index; CRF, cardiorespiratory fitness; FEP, first-episode psychosis; HC, healthy controls; HR, heart rate; IHD, ischemic heart disease; n, number; SD, standard deviation; YMCA, Young Men's Christian Association.

†Baseline data on continuous variables are reported as mean ± SD, VO_2 measured in $mlO_2/kg/min$, and BMI is measured in kg/m^2 unless otherwise stated.

‡Median scores were reported in Nyboe et al (8), but mean scores were available in other papers by Nyboe and colleagues.

male (15, 16). By contrast, the cross-sectional studies included a total of 2698 cases (across Stages 1–4) and 3129 HC and all except one of these studies (35) comprised 55–100% males. The median sample age was about 33 years, and 13 studies reported the inclusion of affective or schizoaffective alongside non-affective psychoses (17, 20, 22, 25, 27–29, 32, 33, 35–37, 41).

Only one study reported CRF findings for a subsample classified as Stage 0 (122 individuals with a family history of psychosis) (13); two studies reported CRF findings in samples classified as Stage 1 (13, 14). For Stage 2, three cohort studies reported CRF in army recruits and noted an association between lower CRF and the incidence of FEP (15–17); two other studies employed a case–control design (8, 14) and six others comprised of FEP groups only (18–23). Nineteen studies included subgroups classified as Stage 3 (24–42), of which four included a matched HC group (30–32, 40) and one included a general population reference sample (39). Seven studies included subgroups classified as Stage 4 (43–49), of which two included matched HC groups (45, 46).

The median study quality rating was 8, reflecting that most publications were graded as fair (n = 18). There was no pattern to the identified weaknesses, although some studies failed to report the technique for assessing CRF or used less robust measurements (detailed ratings available from the authors on request). Other studies had a range of potential design or methodological biases or disadvantages (e.g., convenience sampling, small N, single-arm studies, lack of data on potential confounders).

Despite methodological limitations across studies, descriptive synthesis of findings indicated that suboptimal CRF was observed in Stage 0 (offspring), Stage 1 (CHR/UHR), and Stage 2 (FEP) including evidence from incidence studies (13, 15, 16) and case–control comparisons (8, 14). Likewise, impaired CRF was reported in clinical samples classified as Stage 3 or 4 compared with matched HC (30–32, 40, 45, 46). Many case–control studies matched groups for demographic variables known to influence CRF but not for BMI. The latter was often higher in established cases than HC (32), and some studies targeted patients who were clinically obese (who are more likely to have impaired CRF (26). Furthermore, where CRF was reported separately according to sex (in the original study), there was a trend for female subgroups to show a smaller difference in mean CRF scores between cases and controls (than male cases vs. male controls) (49).

Table 2. Eligible studies that include cases classified as Stage 3 or 4

Study (1st author; year of publication; location; reference number)	Design	Cases†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Stage 3 studies						
Beebe LH [2005], USA (24)	Cross-sectional (case series)	10 (8 males) cases with DSM-IV schizophrenia; age ranged from 40 to 63 years (mean of 42); BMI ~32.5	6MWT	1394 m (SD not reported)		
Marzolini [2009], Canada (25)	Cross-sectional (2-arm RCT)	13 (8 males) cases with DSM-IV schizophrenia or schizoaffective disorder; age 44.6 ± 3years; BMI = 28.2 ± 2.0	6MWT	525 ± 27 m		
Strassnig [2011], Canada (26)	Cross-sectional	117 (46 males) obese community-based patients with DSM-IV schizophrenia; age 45.1 ± 10.1 years; BMI = 36.7 ± 7.5	Cycle ergometer test with CPX. Modified Bruce protocol	VO_2 max = 15.5 ± 6.1 (42 ± 11% of the age and sex norms predicted VO_2 max)		
Vancampfort [2011], Belgium (27)	Cross-sectional	106 (69 males) with DSM-IV schizophrenia or schizoaffective disorder with/without metabolic syndrome; age 35.4 ± 10.4 years; BMI = 25.5 ± 5.6	6MWT	587 ± 108 m		
Battaglia [2013], Italy (28)	Cross-sectional (2-arm RCT)	18 males with DSM-IV schizophrenia or schizoaffective disorder; age 35.6 ± 4.5 years; BMI = 28.6 ± 3.4	30-m sprint run test and slalom test running with ball	30 m; ≈5.8 ± 0.4 s, slalom; ≈7.0 ± 1.0 s		
Bredin [2013], Canada (29)	Cross-sectional (case series)	13 (7 males) individuals with DSM-IV schizophrenia or schizoaffective disorder; age 30.9 ± 7.2 years; BMI = 29.0 ± 6.0	Cycle ergometer test with CPX	VO_2 peak = 20.5 ± 11.1 (57 ± 25% of the age and sex norms predicted VO_2 max)		
Ozbulut et al. [2013], Turkey (30)	Cross-sectional (case–control)	60 (30 males) cases with DSM-IV schizophrenia; age 35.2 ± 12.2 years; BMI = 28.1 ± 5.3	Astrand submaximal cycle ergometer test	VO_2 max = 29.0 ± 9.0	60 matched HC	VO_2 max = 31.9 ± 7.4
Scheewe [2013], the Netherlands (31)	Cross-sectional (2-arm RCT, plus case–control)	63 (46 males) with DSM-IV schizophrenia spectrum disorders; age 29.6 ± 7.4 years; BMI = 26.3 ± 6.0	Cycle ergometer test with CPX	VO_2 peak = 31.6 ± 9.9	55 matched sedentary HC	VO_2 peak = 35.9 ± 5.5
Kimhy et al. [2014], USA (32)	Cross-sectional (case–control)	32 (20 males) individuals with DSM-IV schizophrenia (*N* = 25) or schizoaffective disorder (*N* = 7); age 37.3 ± 9.4years; BMI = 32.1 ± 6.1	Cycle ergometer test with CPX	VO_2 max = 21.5 ± 6.5	64 matched HC	VO_2 max = 28.9 ± 7.0

Table 2. (Continued)

Study (1st author; year of publication; location; reference number)	Design	Cases†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Bartels [2015], USA (33)	Cross-sectional (2-arm RCT)	210 (103 males) cases with serious mental illness (DSM-IV schizophrenia (*N* = 49), schizoaffective disorder (*N* = 68), bipolar (*N* = 60) and axis I diagnosis of major depression (*N* = 33)); age 43.9 ± 11.2 years; BMI = 36.8 ± 8.2	6MWT	406.6 ± 88.5 m		
Gomes [2016], Portugal (34)	Cross-sectional (case series)	51 (39 males) cases with DSM-IV schizophrenia; age 39.9 ± 7.1 years; BMI = 29.1 ± 4.8	6MWT, 13 cases performed a peak treadmill test with CPX	547 ± 71 meters VO_2 max = 29.0 ± 4.9 (*n* = 13)		
Speyer [2016], Denmark (35)	Cross-sectional (3-arm RCT)	428 (188 males) with ICD-10 schizophrenia (*N* = 377), schizoaffective disorder or persistent delusional disorder; age 39 ± 12 years; BMI = 34.2 ± 6.0	Cycle ergometer with CPX	VO_2 max = 17.4 ± 5.5		
Su [2016], Taiwan (36)	Cross-sectional (2-arm RCT)	44 (20 males) with DSM-IV schizophrenia or schizoaffective disorder; age 31.5 ± 10.3 years	Treadmill walk test (Bruce protocol), estimated VO_2 max	VO_2 max = 31.0 ± 9.9		
Yoon [2016], Korea (37)	Cross-sectional (case series)	24 (15 males) individuals with DSM-IV schizophrenia (*N* = 19) or schizoaffective disorder (*N* = 5); age 39 ± 13 years; BMI = 27.5 ± 6.7	YMCA 3-minute step test	132.8 ± 27.2 beats during the first minute after completing test		
Cheng [2017], Taiwan (38)	Cross-sectional (2-arm RCT)	54 (42 males) with DSM-IV schizophrenia; 45.6 ± 11.3 years; BMI = 25.1 ± 4.5	3-minute step test	37.1 ± 20.6 m		
Andersen [2018] Norway (39)	Cross-sectional	67 (37 males) with DSM-5 schizophrenia spectrum disorder: 37 ± 13 years; BMI = 29.4 ± 5.7	Peak treadmill test with CPX	VO_2 peak = 24 ± 8	2809 (1517 males) from population-based sample	VO_2 peak = 31±7
Brobakken [2018], Norway (40)	Cross-sectional (case–control)	48 (28 males) with ICD-10 schizophrenia, schizotypal or delusional disorders; 35 ± 11 years; BMI = 26.0 ± 6.1	Peak treadmill test with CPX	VO_2 peak = 31.1 ± 8.9	48 matched HC	VO_2 peak = 43.4 ± 7.7

Table 2. (Continued)

Study (1st author; year of publication; location; reference number)	Design	Cases†	CRF assessment	CRF findings—cases†	Comparator†	CRF findings—comparator†
Bueno-Antequera [2018], Spain (41)	Cross-sectional	43 (37 males) with ICD-10 schizophrenia spectrum (*N* = 32) or bipolar disorders (*N* = 11): 42.3 ± 8.5 years; BMI = 30.5 ± 5.5	6MWT	599 ± 95 m		
Perez-Cruzado [2018], Spain (42)	Cross-sectional	62 (37 males) with ICD-10 schizophrenia: 46.2 ± 8.4 years	2-minute step test	110.8 ± 19.4 bpm (after test) 92.9 ± 15.5 bpm (2 min after test) (results based on olanzapine users/non-users)		
Stage 4 studies						
Skrinar [2005], USA (43)	Cross-sectional (2-arm RCT)	20 cases (10 males) with DSM-IV mood or psychotic disorders; age 37.8 ± 9.9 years; BMI 32.3 ± 5.2	Performance time on a graded tolerance test on a cycle ergometer	574.7 ± 210.6 s		
Heggelund [2011], Norway (44)	Cross-sectional (case series)	33 cases (22 males) in- and out-patients with ICD-10 (F20-29); age 34.4 ± 10.6	Peak treadmill test with CPX	VO_2 peak = 36.6 ± 9.6 (79 ± 22% of the age and sex norms predicted VO_2 max)		
Nilsson [2012], Sweden (45)	Cross-sectional (matched case–control)	10 male in- and out-patients with DSM-IV schizophrenia; age 34.7 ± 7.9 years; BMI = 28.5 ± 6.3	Astrand submaximal cycle ergometer test	VO_2 max = 26.4 ± 7.7	10 matched HC	VO_2 max = 45.8 ± 16.0
Ostermann [2013], Germany (46)	Cross-sectional (matched case–control)	23 cases (17 males) with DSM-IV schizophrenia; age 28.2 ± 4.1 years; BMI = 23.6 ± 2.7	Cycle ergometer test with CPX	VO_2 peak = 27.1 ± 6.2	23 matched HC	VO_2 peak = 36.1 ± 8.1
Vancampfort [2014], Belgium (47)	Cross-sectional (case series)	47 (34 males) cases with DSM-IV schizophrenia; age 34.2 ± 11.1 years; BMI = 25.8 ± 4.3	Astrand submaximal cycle ergometer test	VO_2 max predicted = 34.6 ± 8.7		
Kim [2014], Korea (48)	Cross-sectional (2-arm RCT)	36 cases with DSM-IV schizophrenia; age 49.4 ± 10.5 years, BMI = 25.5 ± 4.4	YMCA 3-min step test	121.8 ± 12.0 beats during the first minute after completing test		
Curcic [2017], Serbia (49)	Cross-sectional (2-arm RCT)	80 in-patients (42 males) with any non-affective psychosis; age 40.8 ± 9.5; BMI = 26.5 ± 2.7	Treadmill walking test	VO_2 max: males = 21.9 ± 2.3; females = 18.9 ± 1.6		

BMI, body mass index; CPX, cardiopulmonary exercise testing; CRF, cardiorespiratory fitness; DSM, Diagnostic and Statistical Manual; HC, healthy controls; HR, heart rate; ICD, International Classification of Diseases; *n*, number; 6MWT, six-minute walk test; SD, standard deviation; YMCA, Young Men's Christian Association.

†Baseline data on continuous variables are reported as mean ± standard deviation, VO_2 measured in $mlO_2/kg/min$, and BMI is measured in kg/m^2 unless otherwise stated.

Meta-analyses

Twenty-two studies (8, 13, 14, 16, 18, 20–23, 26, 29–32, 35, 36, 39, 40, 44–47, 49) reported CRF data as mean scores for VO_2 (max, peak, or predicted VO2 in ml/kg/min), and 10 of these studies included data for HC (Stage 1 = 1; Stages 1 and 2 = 1; Stage 2 = 2; Stage 3 = 5; Stage 4 = 2). Figure 2 reports the sample sizes for each group in the 10 eligible studies, and the forest plot demonstrates the overall ES for CRF (with 95% CI) for all studies (8, 14, 16, 30–32, 39, 40, 45, 46) and then the ES for each clinical stage. The overall ES (shown at the bottom of the plot) highlights that CRF was significantly reduced when samples comprising of individuals classified according to stage were combined together (N = 637) compared with the 5606 controls (random-effects model: g = −0.93; 95% CI −1.14, −0.71). The estimated ES for analyses according to clinical stage suggest that mean CRF was non-significantly decreased in the one study that compared individuals classified at Stage 1 and controls (g = −0.79; 95% CI −1.71, +0.13), but was significantly impaired in cases meeting criteria for Stage 2 (g = −0.96; 95% CI −1.43, −0.49), Stage 3 (g = −0.85; 95% CI −1.19, −0.5), and Stage 4 (g = −1.32; 95% CI −2.06, −0.58) compared with controls. There was evidence of statistical heterogeneity in the pooled ES (Q = 32.12; P = 0.001; I^2 = 68.67), but Egger's regression test (Z value = 15.35; P = 0.0001), the funnel plot (see Figure S1 in Appendix S4), and the fail–safe N (required N = 665) did not indicate any publication bias. Meta-regression analyses (see Figure S2 in Appendix S4) suggested that mean age and proportion of males in a sample were significantly associated with a larger ES. The same trend (P = 0.08) was observed for the regression of BMI on Hedges' g, but data from some studies could not be included in this regression model (16). Sensitivity analyses were feasible for studies that used cycle ergonomic tests to assess VO_2 or studies of samples that included non-affective psychoses only, but these approaches made minimal differences to the magnitude of the reported ES.

Figure 3 shows a diagrammatic representation of the mean values for VO_2 according to HC or stage of illness (no relevant data were available for Stage 0) with the ES for the difference in VO_2 for each pair of comparisons; the forest plot is shown in the online supplementary materials (Figure S3 in Appendix S4). These analyses included data from four HC samples (N = 5586), one sample classified as Stage 1 (N = 10), eight as Stage 2 (N = 509), ten as Stage 3 (N = 457), and three as Stage 4 (N = 73). As shown, there is an incremental decrease in mean VO_2 from 40.95 (SD = 6.85) in HC to 24.66 (SD = 3.63) ml/kg/min in Stage 4 cases. The ES (Hedges' g) for each pairwise decrease in VO_2 were as follows: −1.00 (95% CI −1.62, −0.38) from HC to Stage 1; −0.58 (95% CI −1.21, +0.04) from Stages 1–2; −1.16 (95% CI −1.31, −1.03) from Stages 2–3; and −0.08 (95% CI −0.33, +0.16) from Stages 3–4. There was evidence of moderate statistical heterogeneity in the pooled ES for the Stage 3 vs. 4 analysis (Q = 27.13; P = 0.003; I^2 = 53.71). Only one sensitivity analysis was possible for these data, namely an examination of degree of certainty regarding the classification of samples according to clinical stage. This analysis showed that the ES for the difference in mean CRF between Stages 3 and 4 increased marginally (ES −0.24; 95% CI −0.51, +0.01) when three Stage 3 studies were excluded from this analysis (29, 36, 42). Across Stages 1–4, there was an increase in mean age (from 21 to 32 years) and BMI (from 24 to 28 kg/m^2), but the mean proportion of males decreased across Stages

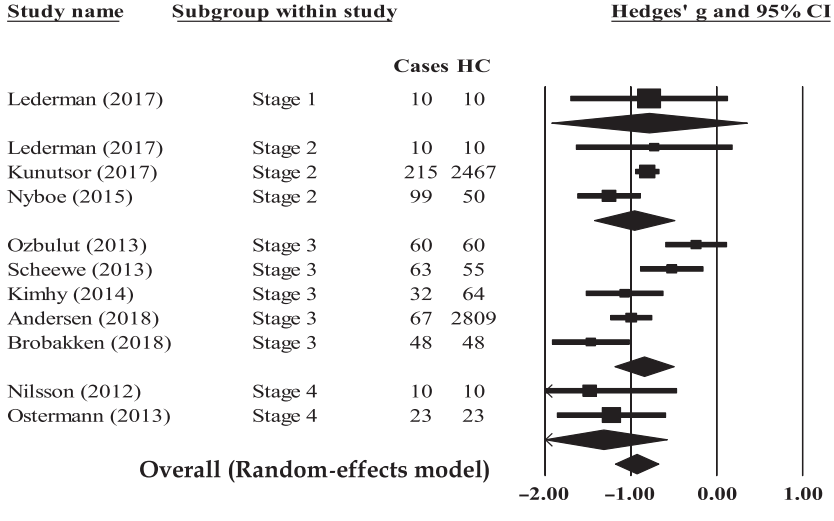
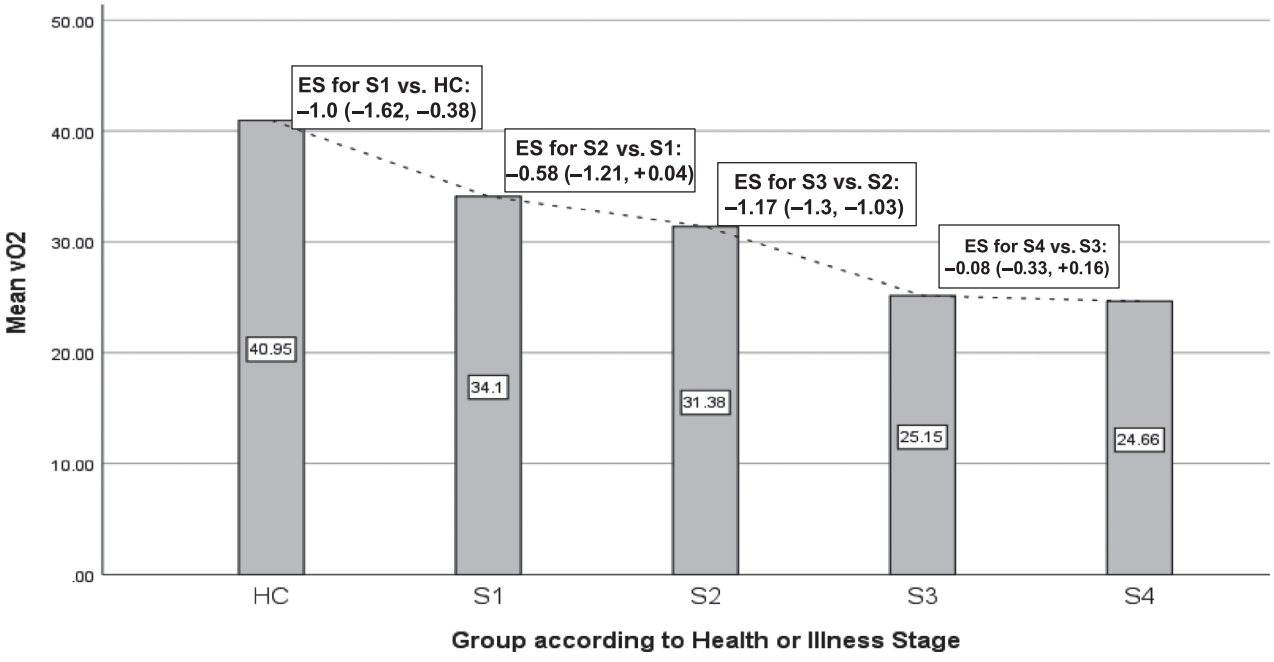


Fig. 2. Meta-analysis of CRF and clinical stage (cases) in comparison with healthy controls (HC). Box size represents study weighting, diamonds represent pooled effect size (ES measured as Hedges' g with 95% confidence intervals) by stage, and diamond at the base of the figure represents overall ES for included studies.



Individuals per category: HC = 5586; S1 = 10; S2 = 509; S3 = 457; S4 = 73

Fig. 3. Diagrammatic representation of mean VO_2 (max or predicted measured in ml/kg/min) in pooled samples of healthy controls (HC) or classified according to clinical stage (S1–S4). The effect size (ES) for difference in VO_2 is reported between sequential pairs, for example, S1 vs. HC, S2 vs. S1 (see text for details and Figure S3 for classic forest plot of these data).

1–4 (from 0.8 to 0.7). The meta-regression analyses did not identify any significant associations with age, sex distribution, or BMI, although there was a trend toward significance for BMI ($P = 0.07$).

Discussion

Our meta-analysis is the first to compare objectively assessed CRF in individuals at Stages 0–4 of psychotic disorders with general population or HC groups. The data show that CRF was significantly lower in individuals at any stage of illness compared with controls (overall ES −0.93). Looking at each pooled analysis according to stage of psychosis, we show that CRF is non-significantly decreased in Stage 1 compared with control populations ($g = -0.79$; 95% CI −1.71, +0.13), but significantly impaired in Stage 2 ($g = -0.96$), Stage 3 ($g = -0.85$) and Stage 4 ($g = -1.32$). Further, when we examined differences across HC and Stage 1, and then across clinical stages (pairwise analyses Stage 1 vs. 2, etc.), we were able to demonstrate that there is an incremental decrease in mean VO_2 from 40.95 (SD = 6.85) in HC to 24.66 (SD = 3.63) ml/kg/min in Stage 4 cases, with moderate to large ES between each clinical stage. The level of impairment in CRF was significantly reduced between HC and Stage 1 and between Stages 2 and 3, with a trend toward significance between Stages 1 and 2, but very little difference in CRF between Stages 3 and 4 (see Figures 3 and Figure S3). These CRF decreases are from a clinical perspective very important, as CRF primarily measures aerobic energy capacity and every 3.5 ml/kg/min decrease in VO_2 is associated with a 13% and 15% increase in the risk of all-cause premature mortality and cardiovascular disease-associated premature mortality respectively (6). Importantly, evidence indicates that engaging in a range of aerobic physical activities can improve CRF, but also reduce psychiatric symptoms and improve neurocognitive and social functioning.

The large ES reported here for the differences in objectively assessed CRF in individuals identified as being at risk of psychosis and/or meeting criteria for clinical caseness compared with controls (and outputs from the meta-regression analyses) confirm previous findings from similar reviews of physical health markers in individuals with major mental disorders (7, 10, 50) and support demands for the wider implementation of interventions that target the physical fitness and wellbeing of individuals with psychotic and mood disorders (51). However, our approach extends previous research in two important aspects. First, the narrative review (alongside data summarized in Table 1) highlights that lower CRF may be associated with the earliest

stages of psychosis, including asymptomatic at-risk states (Stage 0) and medication-naïve conditions that do not meet diagnostic criteria for an affective or non-affective psychotic disorder (Stage 1). There were too few eligible studies to explore these issues in greater depth, but the observed trends suggest that, at the very least, we should not assume that impaired CRF is exclusively associated with psychotic disorders meeting diagnostic criteria or the putative consequences of that diagnosis (use of medication and reduced daytime activity, etc.). Further, the current findings taken together with our previous systematic review (9) emphasize that reduced CRF is associated not only with transition from subthreshold to full threshold psychotic disorders, but also with new onsets of a wide range of adverse mental health outcomes, including increased risk of suicide attempts, first-episode mania. So, while the focus of this review was on CRF and stages of illness in psychosis, it can be argued that CRF impairment is unlikely to be uniquely associated with psychosis only; indeed (given the possibility of heterotypic illness outcomes for Stages 0 and 1) (1, 2), it is highly likely that our findings will be replicated in future transdiagnostic studies of staging models. Importantly, the current findings support the importance of a wider public health strategy regarding physical fitness that incorporates universal and indicated interventions, as it appears that higher levels of CRF may be associated with reduced or delayed risk of onset or progression of both mental and physical disorders. Second, our qualitative and quantitative findings indicate that cases of FEP (Stage 2) and established illness (Stages 3 and 4) have significantly reduced CRF compared to controls and we demonstrated a 28% reduction in mean VO_2 between Stage 1 and Stage 4 samples (as shown in Figure 3: VO_2 dropped from 34.1 to 24.63 ml/kg/min), with the largest ES ($g = -1.16$) for the decrease in CRF between Stages 2 and 3 (i.e., FEP vs. established psychotic disorder). It should be emphasized that our findings do *not* imply a direct causal link between disease progression and CRF. However, they do suggest a critical need for early intervention programmes to address the physical wellbeing of youth from the moment they access services for an emerging mental disorder (52), but also offer a timely reminder that assertive outreach programmes for individuals with late-stage psychosis should be encouraged to screen more rigorously for impaired CRF or other risk factors for physical disorders especially as the research indicates that 20–40% of late-stage patients have an aerobic capacity below that required for functional daily living (6, 29).

The strengths of this meta-analysis are the novel application of a clinical staging model of psychosis to compare CRF across the entire illness continuum from asymptomatic at-risk state to late-stage disease and the emphasis on objective assessments of CRF (with mean VO_2 being selected as the variable of interest for pooled quantitative analyses). However, there are also limitations. For example, few publications of physical fitness and psychosis specifically refer to illness stage and so it is possible our search criteria failed to identify some eligible studies. We could not include any data for Stage 0 in the meta-analyses (and we were unable to determine whether any of the putative Stage 0 cohort had any psychotic or non-psychotic symptoms). Also, the only eligible Stage 1 sample was very small ($N = 10$); this created a number of issues in terms of the representativeness of that data, but also because we could only examine these data from the perspective of presumed risk of psychosis (which is not the only adverse mental health outcome for UHR or CHR populations). Insufficient data were available to examine any effects of medications, coexisting physical disorders, nicotine consumption, or other risk factors for cardiorespiratory conditions in study samples or according to sex. Most studies were cross-sectional, so it is not possible to examine whether disease progression (change in illness stage) is causally associated with disease extension (worsening of CRF). Also, while there is increasing consensus regarding definitions of each clinical stage of psychosis, we had to translate existing heuristic frameworks into criteria that could be used to reliably classify study samples according to stage of illness. While operationalization of the criteria for Stages 1–2 was relatively self-evident, we were unable to further subclassify Stage 1 studies (some researchers argue that Stage 1 can be subdivided, for example, into Stage 1a and 1b according to specificity of symptom patterns). Previous publications (even those addressing staging in psychosis) often merge Stages 3 and 4 into a single 'late-Stage' category. The lack of consistent definitions of the boundary between Stages 3 and 4 in current models of psychosis or their dependence on some information that was absent from the data sets of most CRF studies we screened (e.g., functioning and/or neuropsychological variables) challenged our ability to classify some study populations. As such, the potential over-reliance on proxies related to illness duration and health service use (out- vs. in-patient status) means we were least confident about classifying samples as Stage 3. Having

noted that issue, we did demonstrate that CRF in Stage 3 is marginally higher than in Stage 4, and findings from sensitivity analysis and the evidence of statistical heterogeneity should be noted.

Regarding CRF, we chose this measure of fitness as it can be tested objectively (e.g., cycle ergonomic tests, treadmill walk tests), and as such has significant advantages over self-ratings or clinician-rated scales (which routinely over-estimate physical activity by 30–50%) (9). However, CRF assessments are fallible and (although the sensitivity analyses did not demonstrate a significant change in ES when we excluded some studies using less commonly employed assessments, e.g., 6MWT) it is important to acknowledge that CRF assessments have different relative reliabilities (11). Also, there were insufficient data to allow separate pooled analyses of studies reporting the maximum, peak, or predicted VO_2. Like the methods of CRF testing, this is relevant because these three VO_2 parameters are similar but not the same (11).

Part of the impetus for the current study was to determine the feasibility of using a staging framework for testing hypotheses regarding putative links between milestones of disease progression in psychosis (i.e., clinical stage) and markers of physical fitness or risk factors for medical disorders. The research strategy employed for identifying and analyzing studies of CRF and clinical stages of psychosis demonstrated a plausible association between the two phenomena. We conclude that the approach has promise (and indeed helps expose gaps, the lack of research on CRF and early stages of psychotic disorder). However, the findings must be viewed in the context of the modest quality of most of the eligible studies and we note that the available data did not permit a dynamic assessment of whether decrease in VO_2 over time leads to disease progression or extension, or vice versa. To improve this type of research, it is important to find ways to encourage investigators to consider recording stage of illness in future studies of psychosis and all other major mental disorders and any associations with physical health or illness (1–3). A preliminary scoping exercise suggested that currently, there are more data on psychotic than depressive or bipolar disorders, and this limits the opportunities to examine staging in each mood disorder, but also means it is not feasible to extend the current meta-analytic approach to study transdiagnostic staging models. On a positive note, some of the findings reported here, such as potential evidence of impaired CRF in populations at risk of psychosis, may promote the generation of new hypotheses about the inter-relationships between physical and mental health markers and epigenetic influences (53) and whether markers of physical wellbeing (such as CRF or metabolic health) can be used to help elucidate the clinic–pathological boundaries between illness stages in mental disorders. This is worthwhile as it may enhance understanding of how disease extension can be mapped onto staging models and develop the staging framework beyond notions of typical psychopathology, functioning, and neuropsychology (1–3).

To summarize, using a published clinical staging model of psychosis, the current systematic review and meta-analyses demonstrate that, compared with matched or general population controls, an impaired CRF is already present at the earliest stages of psychotic disorders, including asymptomatic at-risk states, UHR and CHR presentations, and medication-naïve subthreshold conditions, and demonstrate an apparent stepwise worsening across each stage of illness. If our findings are confirmed in future studies, then it may lead to a greater understanding of the nature of the inter-relationships between physical wellbeing, risk factors for physical disorders and onset and progression of severe mental disorders. Clinically, a major implication of this project is that it seems that impaired CRF (compared to population norms) coexists with the emergence of psychotic disorders and supports the need for early interventions to address both mental and physical wellbeing. Further, given that CRF is even lower in late-stage psychosis, the recommendation for regular monitoring in routine clinical assessments seems justified.

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Declaration of interest

MJT is the unpaid Chair and co-founder of 'Us' (a charity for young people with or at risk of developing mental illness that provides opportunities to become involved with in sport and exercise). JS is a visiting professor at NTNU, Trondheim; Diderot University, Paris; and the Brain and Mind Centre at the University of Sydney.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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This is an abbreviated list of references; additional references that are of relevance are provided in Appendix S5.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Staging Models: heuristic framework for clinical stages of psychotic disorders- see main text for details (as described in e.g. McGorry et al (1), Scott et al (2)).
Appendix S2. PRISMA checklist.
Appendix S3. Example of electronic search strategy.
Appendix S4. Supplementary Analyses and meta-regressions.
Appendix S5. Additional references.