Associations of Leisure-Time and Occupational Physical Activity and Cardiorespiratory Fitness With Incident and Recurrent Major Depressive Disorder, Depressive Symptoms, and Incident Anxiety in a General Population

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ABSTRACT

Objective: Physical activity and cardiorespiratory fitness may help prevent depression and anxiety. Previous studies have been limited by error-prone measurements. We examined whether self-reported physical activity domains and peak exercise capacity ($peakVO_2$) are associated with incident and recurrent major depressive disorder (MDD), depressive symptoms, and anxiety disorders.

Methods: This was a prospective population-based study of 1,080 adult men and women (25–83 years) with a median follow-up of 4.5 years and measures of physical activity during leisure time, sports, and work (Baecke questionnaire); a measure of depressive symptoms (Beck Depression Inventory II); symptom-limited cycle ergometer testing ($peakVO_2$, oxygen uptake at anaerobic threshold [VO_2@AT], maximum power output at peak exertion); and a structured psychiatric interview (Munich Composite International Diagnostic Interview). Baseline data were collected between 2002 and 2006, and follow-up data, between 2007 and 2010.

Results: After adjustment for age, sex, education, smoking, alcohol consumption, and waist circumference, the relative risks for incident MDD per standard deviation (SD) increase in leisure-time physical activity, physical activity during sport, physical activity at work, $peakVO_2$, VO_2@AT, and maximum power output were 1.002 (95% confidence interval, 0.90 to 1.12), 1.02 (0.90 to 1.15), 0.94 (0.80 to 1.10), 0.71 (0.52 to 0.98), 0.83 (0.66 to 1.04), and 0.71 (0.52 to 0.96), respectively. $PeakVO_2$, VO_2@AT, and maximum power output were associated with recurrent MDD, depressive symptoms, and anxiety. $PeakVO_2$ was more strongly related to the co-occurrence of MDD and anxiety (adjusted odds ratio [OR] = 0.45 [0.24 to 0.84]) than depression or anxiety alone (OR = 0.71 [0.53 to 0.94]).

Conclusions: Greater cardiorespiratory fitness but not domain-specific physical activity was associated with a lower incidence of MDD and clinical anxiety.

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Population-based, prospective studies provide substantial evidence that regular physical activity (PA) is inversely associated with the onset of depressive symptoms and major depressive disorder (MDD).[1–5] Population-based studies suggest that people who are regularly physically active have 45% lower odds of onset of MDD and between 28%–48% lower incidence of anxiety disorder.[3] A meta-analysis of randomized trials found a modest protective effect of PA on depression and a small effect on anxiety in nonclinical adult populations.[4] However, available research provides little quantitative support for specific recommendations regarding the most beneficial duration, intensity, frequency, mode, or domains of PA (leisure time, occupational, transportation, domestic).[2,4,6] Previous population-based cohort studies have focused on leisure-time PA alone or total PA (ie, the combination of domain-specific PA).[2,4,5] Only a few cross-sectional studies compared leisure-time PA with PA in other domains and found that leisure-time PA is more strongly associated with depressive symptoms than PA in other domains.[5,7]

Cardiorespiratory fitness (CRF) is a measure of the capacity of the cardiovascular system to transport oxygen and the capacity of the muscle to use it.[8,9] Low CRF is a well-recognized risk factor for coronary heart disease and cardiovascular mortality.[8–11] It is well known that regular PA increases CRF,[8,9,12] and given the beneficial effects of PA and exercise on depression and anxiety,[4,13,14] it is to be expected that CRF is inversely related to depression and anxiety. The relationship between CRF and depressive symptoms has been studied in several cross-sectional and prospective studies.[15–23] A meta-analysis of experimental and observational studies found a modest correlation between CRF and depressive symptoms[24] in healthy subjects. The meta-analysis[24] revealed limitations of existing studies: first, most studies used indirect estimations of CRF (eg, time[20,22] or workload[25] of the exercise test), and only 2 smaller cross-sectional studies[16,26] used a submaximal symptom-limited cardiopulmonary exercise test to measure peak oxygen uptake ($peakVO_2$) for assessment of CRF.[24] $PeakVO_2$ is considered the reference standard for CRF.[8,9,12,27] Second, previous studies used symptoms

Clinical Points

- This study found inverse relations of physical activity and cardiorespiratory fitness to depressive symptoms, incident and recurrent major depressive disorder, and anxiety.
- These findings should stimulate further clinical, intervention, and prognostic research on the effects of exercise on mental health.

scales[20,22,23] for measurement of depressive symptoms or hospital records of treated depression.[25] Unfortunately, measurement error of depression may vary by level of CRF, which might induce differential measurement error.[28]

The present study expands on previous studies using prospective data from the population-based Study of Health in Pomerania (SHIP)[29] to further assess the relations between domain-specific PA and CRF with depression and anxiety using direct measures of CRF (ie, peakVO_2, oxygen uptake at anaerobic threshold [VO_2@AT], maximal power output) and MDD and anxiety disorder based on a well-established structured psychiatric interview.

METHODS

Study Population

SHIP is a population-based prospective cohort study of adult residents (20–79 years) in northeastern Germany. A sample of 6,265 eligible individuals was drawn from local population registries, and 4,308 (2,192 women) participated at the first examination (SHIP-0) between 1997 and 2001 (response of 69%). A second examination cycle (SHIP-1) was conducted between 2002 and 2006 and comprised 3,300 participants. In SHIP-1, self-reported PA was assessed in 3,255 individuals, and 1,575 subjects volunteered for CRF testing. The SHIP-1 examination cycle was therefore defined as the baseline examination for the present analyses. Between 2007 and 2010, a third examination, the Life-Events and Gene-Environment Interaction in Depression (LEGEND) study, with standardized psychiatric interviews was performed.[29] To reduce possible bias due to reverse causation, we restricted the analyses to participants without a history of depressive symptoms, anxiety symptoms, lung disease, or asthma at SHIP-1. All participants gave written informed consent, and the Ethics Committee of the University of Greifswald approved the study protocol.

Assessments

At the follow-up, MDD, recurrent MDD, and anxiety (panic disorder, agoraphobia, generalized anxiety disorder, social phobia, specific phobias) were diagnosed according to *DSM-IV* using the Munich-Composite International Diagnostic Interview (M-CIDI).[30–32] The interviews were conducted by experienced clinical psychologists in a face-to-face situation. Current depressive symptoms over the past 2 weeks prior to the LEGEND examination date were assessed using the German version of the Beck Depression Inventory-II (BDI-II).[33,34] The BDI-II score was constructed by summing the highest ratings for each of 21 symptoms, and it ranged from 0 to 41. We used the BDI-II (< 12 vs ≥ 12)[35] as a binary outcome and the BDI-II sum score as a continuous outcome. The Composite International Diagnostic Screener (CID-S)[36] was used to exclude participants with a history of symptoms of depression and anxiety at baseline.

At baseline, PA was assessed using the Baecke questionnaire[37] during a computer-assisted interview. It consists of 16 items organized in 3 sections: PA at work, sports during leisure time, and PA during leisure time excluding sport, scored on a 5-point Likert scale, ranging from never to always or very often. The 3 derived indices (Leisure Time, Sports, Work) are scored in arbitrary units ranging from 1 to 5. Retest reliability ranges between 0.65 and 0.92, and correlation with doubly labeled water is strong.[38–41] A symptom-limited exercise test using a calibrated electromagnetically braked cycle ergometer with an electrical seat height adjustment (Ergoselect 100, Ergoline, Germany) was performed according to a modified Jones protocol: 3 minutes of rest, 1 minute of unloaded cycling at 60 revolutions per minute, stepwise increases in work load of 16 W per minute until symptom-limited or terminated by a physician due to chest pain or electrocardiogram (ECG) abnormalities, and 5 minutes of recovery.[42] Gas exchange and ventilatory variables were analyzed breath by breath averaged over 10-second intervals using a VIASYS HEALTHCARE system (Oxycon Pro, Combitox mask). In the absence of chest pain and ECG abnormalities, all tests were continued as symptom-limited (volitional exertion, dyspnea, or fatigue). PeakVO_2, VO_2@AT, and maximal power output were determined as previously described.[43]

Statistical Analyses

Selected baseline characteristics were compared across quartiles of the Baecke indices and peakVO_2 using age-adjusted means for continuous and age-adjusted percentage values for categorical variables. The associations of Baecke indices, peakVO_2, VO_2@AT, and maximum power output (modeled as continuous covariates) with incident MDD, recurrent MDD, and anxiety and BDI-II score ≥ 12 were examined using relative risks (RRs) and 95% confidence intervals from Poisson regression with robust standard errors and time between measurements set as offset.[44] As dichotomizing the BDI-II might have resulted in misclassification bias, we additionally modeled the 88th percentile of the BDI-II sum score, which corresponds to a BDI-II score of 12 (a common cutoff[35]) in the sample, using a quantile regression model.[45] To account for possible nonrandom selection into the working population (ie, retired, unemployed), we used sample selection Poisson regression[46] and quantile regression with sample selection,[47] when the Work index was an exposure. Odds ratios (ORs) for single versus co-occurring incident MDD and anxiety were derived from multinomial logistic regression. We reported 1 model adjusted for baseline age and sex and a fully adjusted model (age, sex, years of schooling, smoking, alcohol consumption, waist circumference). We established linearity

Table 1. Age-Adjusted Selected Baseline Characteristics of the Study Sample by Self-Reported Physical Activity and Peak Oxygen Uptake[a]

	Q1	Q2	Q3	Q4	*P* (Linear Trend)[b]
Baecke Leisure Time Index (N = 1,952)					
N (min–max)	519 (1.0–2.8)	590 (2.9–3.3)	526 (3.4–3.8)	317 (3.9–5.0)	
PeakVO_2, mL/min	2,025.6	2,046.9	2,065.5	2,008.0	.417
VO_2@AT (mL/min)	1,109.3	1,127.1	1,163.0	1,146.7	.049
Maximum power output, W	155.1	159.4	160.9	159.1	.031
Women, %	48.2	46.6	51.6	54.9	.026
School education, % < 10 y	37.5	36.3	33.2	35.0	.239
Current smoker, %	32.5	29.3	24.3	23.7	.004
Alcohol consumption, g/d	11.2	10.0	9.6	9.2	.141
Waist circumference, cm	94.3	92.7	91.8	89.7	< .001
Baecke Sports Index (N = 1,952)					
N (min–max)	705 (1.0–2.0)	292 (2.1–2.3)	611 (2.5–3.0)	344 (3.1–5.0)	
PeakVO_2, mL/min	1,929.6	2,015.9	2,038.1	2,255.8	< .001
VO_2@AT, mL/min	1,079.0	1,107.4	1,141.8	1,249.7	< .001
Maximum power output, W	147.8	155.4	160.2	178.2	< .001
Women, %	49.4	48.7	53.3	44.7	.295
School education, % < 10 y	45.7	36.6	29.1	24.6	< .001
Current smoker, %	30.7	36.3	24.0	21.5	< .001
Alcohol consumption, g/d	9.3	12.1	9.4	11.2	.551
Waist circumference, cm	94.	93.0	91.2	89.1	< .001
History of cardiovascular disease, %	2.4	3.2	1.3	1.7	.346
History of cancer, %	4.4	3.6	5.7	3.8	.629
Baecke Work Index (N = 1,043)					
N (min–max)	265 (1.0–2.1)	317 (2.2–2.9)	209 (3.0–3.4)	252 (3.5–5.0)	
PeakVO_2, mL/min	2,190.0	2,182.9	2,221.5	2,166.0	.293
VO_2@AT, mL/min	1,168.7	1,193.1	1,188.7	1,146.2	.343
Maximum power output, W	175.6	172.0	174.8	168.9	.051
Women, %	56.6	54.2	51.7	41.8	< .001
School education, % < 10 y	5.5	12.1	11.5	25.1	< .001
Current smoker, %	30.0	28.2	31.1	47.2	< .001
Alcohol consumption, g/d	10.0	10.5	10.0	13.0	.032
Waist circumference (cm)	88.3	89.9	87.4	90.3	.068
PeakVO_2 (mL/min) (N = 1,080)					
N (min–max)	270 (800–1,570 mL/min)	270 (1,571–1,937 mL/min)	270 (1,938–2,435 mL/min)	270 (2,440–5,137 mL/min)	
PeakVO_2, mL/min	1,346.4	1,752.5	2,162.3	2,891.7	< .001
VO_2@AT, mL/min	840.6	1,037.8	1,193.0	1,488.9	< .001
Maximum power output, W	103.8	138.2	168.2	221.9	< .001
Women, %	87.1	67.7	30.6	3.5	< .001
School education, % < 10 y	50.3	33.5	33.8	19.5	.485
Current smoker, %	23.4	27.1	27.2	27.1	< .001
Alcohol consumption, g/d	4.6	8.2	11.1	17.7	< .001
Waist circumference, cm	86.6	91.1	97.2	97.1	< .001

[a]Entries are adjusted means for continuous variables and adjusted percentages for categorical variables.
[b]Linear trend test across peakVO_2 categories was quantified with Wald test by assigning median values to each category and modeling this variable as a continuous variable in age-adjusted linear and logistic regression.
Abbreviations: AT = anaerobic threshold, Q1–Q4 = quartiles 1 to 4.

of the relations between Baecke indices; peakVO_2, VO_2@AT, and maximum power; and depression/anxiety by fractional polynomials[48] and reported point estimates per standard deviation increase. We tested for multiplicative interaction with age and sex by comparing the −2 log likelihood of a fully adjusted model with and without product terms. Baecke indices and peakVO_2 were inversely related to loss to follow-up in a logistic model ($P < .01$) that also included socioeconomic, behavioral, and clinical predictors. Thus, we weighted regression models by the inverse probability of taking part in LEGEND.[49] Analyses were performed using Stata 14.1 (Stata Corporation, College Station, Texas).

RESULTS

Our analyses were based on 1,952 individuals for analyses of Baecke indices (n = 1,043 for the Work index). During a median of 4.5 years of follow-up, 267 cases of incident MDD, 160 cases of recurrent MDD, 291 cases of incident depressive symptoms, and 366 cases of incident anxiety disorders occurred. For the analyses of CRF outcomes, 1,080 individuals were available; 116 cases of incident MDD, 98 cases of recurrent MDD, 135 cases of depressive symptoms, and 183 cases of anxiety disorders were observed. Baseline characteristics are shown in Table 1.

Table 2. Association Between Self-Report Physical Activity and Cardiorespiratory Fitness With Incident Depression, Depressive Symptoms, and Anxiety[a]

	MDD RR (95% CI)	Recurrent MDD RR (95% CI)	BDI-II ≥ 12 RR (95% CI)	BDI-II Sum Score (88th Percentile) β (95% CI)	Anxiety RR (95% CI)
Baecke Leisure Time Index (per SD)					
Age- and sex-adjusted	0.99 (0.89 to 1.09)	0.98 (0.84 to 1.15)	0.85 (0.77 to 0.94)	−1.13 (−1.91 to −0.36)	0.97 (0.89 to 1.06)
Full adjustment	1.00 (0.90 to 1.12)	0.98 (0.84 to 1.15)	0.89 (0.80 to 0.98)	−0.75 (−1.39 to −0.11)	0.99 (0.90 to 1.08)
P interaction with age, sex	.327, .122	.566, .534	.267, .543	.222, .498	.254, .567
Baecke Sports Index (per SD)					
Age- and sex-adjusted	0.99 (0.88 to 1.12)	0.99 (0.86 to 1.16)	0.78 (0.70 to 0.88)	−1.74 (−2.39 to 1.08)	0.91 (0.83 to 0.99)
Full adjustment	1.02 (0.90 to 1.15)	0.99 (0.98 to 1.16)	0.83 (0.74 to 0.93)	−1.40 (−1.98 to −0.81)	0.92 (0.83 to 1.01)
P interaction with age, sex	.850, .785	.692, .835	.987, .882	.714, .647	.693, .539
Baecke Work Index (per SD)					
Age- and sex-adjusted	0.97 (0.83 to 1.14)	0.98 (0.80 to 1.19)	1.18 (0.99 to 1.41)	1.40 (0.42 to 2.38)	0.99 (0.88 to 1.11)
Full adjustment	0.94 (0.80 to 1.10)	0.97 (0.80 to 1.19)	1.17 (0.97 to 1.39)	1.10 (−0.16 to 2.36)	0.98 (0.87 to 1.11)
P interaction with age, sex	.668, .137	.243, .767	.691, .992	.737, .155	.200, .068
PeakVO$_2$ (per SD)					
Age- and sex-adjusted	0.69 (0.54 to 0.89)	0.66 (0.51 to 0.86)	0.73 (0.59 to 0.91)	−1.45 (−2.10 to −0.81)	0.70 (0.52 to 0.96)
Full adjustment	0.71 (0.52 to 0.98)	0.66 (0.50 to 0.85)	0.68 (0.48 to 0.97)	−1.75 (−2.84 to −0.66)	0.69 (0.50 to 0.95)
P interaction with age, sex	.076, .830	.613, .431	.843, .272	.937, .414	.433, .796
VO$_2$@AT (per SD)					
Age- and sex-adjusted	0.74 (0.56 to 0.98)	0.80 (0.70 to 0.92)	0.88 (0.73 to 1.06)	−0.58 (−1.60 to 0.45)	0.82 (0.68 to 0.98)
Full adjustment	0.83 (0.66 to 1.04)	0.80 (0.71 to 0.91)	0.86 (0.69 to 1.07)	−0.52 (−1.66 to 0.63)	0.79 (0.65 to 0.97)
P interaction with age, sex	.784, .451	.687, .761	.592, .144	.641, .334	.866, .565
Maximum power output (per SD)					
Age- and sex-adjusted	0.67 (0.53 to 0.86)	0.61 (0.47 to 0.78)	0.71 (0.58 to 0.87)	−1.89 (−3.13 to −0.66)	0.72 (0.61 to 0.85)
Full adjustment	0.71 (0.52 to 0.96)	0.69 (0.52 to 0.92)	0.69 (0.53 to 0.89)	−1.34 (−2.65 to −0.04)	0.72 (0.59 to 0.88)
P interaction with age, sex	.029, .769	.761, .765	.928, .911	.455, .753	.859, .803

[a]Potential nonlinear relation of peakVO$_2$, VO$_2$@AT, and maximum power output with depression/anxiety was tested by using second-degree fractional polynomials. Full adjustment included age, sex, years of schooling, alcohol consumption, smoking, and waist circumference. One regression model was run for each exposure-outcome combination.

Abbreviations: AT = anaerobic threshold, β = quantile regression coefficient, BDI-II = Beck Depression Inventory-II, CI = confidence interval, MDD = major depressive disorder, RR = relative risk [adjusted relative risk from a weighted Poisson regression with robust standard errors and ln(time) as offset], SD = standard deviation.

Association of PA Domains With Incident and Recurrent MDD and Depressive Symptoms

The Leisure Time and Sports indices were inversely related to current depressive symptoms but not to incident and recurring MDD (Table 2). The Work index was not significantly associated with incident or recurrent MDD or depressive symptoms. After full adjustment, the RRs for depressive symptoms per 1 standard deviation (1 SD) in the Leisure Time and Sports indices were 0.89 and 0.83, respectively. Likewise, the BDI-II sum score at the 88th percentile decreased by −0.75 and −1.40 points per 1-SD increase in the Leisure Time and Sports indices, respectively. A comparison of RR and quantile regression coefficients (per 1 SD) suggests that the associations of the Sports index with BDI-II ≥ 12 and the BDI-II sum score were slightly stronger than the corresponding associations with the Leisure Time index. Associations were not modified by age or sex, as indicated by nonsignificant interaction terms.

Association of CRF With Incident and Recurrent MDD and Depressive Symptoms

PeakVO$_2$ and maximum power output were inversely associated with incident and recurrent MDD and current depressive symptoms (Table 2). VO$_2$@AT was related to recurrent MDD but not to incident MDD or depressive symptoms. After full adjustment, RRs for incident MDD per 1-SD increase in peakVO$_2$, VO$_2$@AT, and maximum power output were 0.71, 0.83, and 0.71, respectively. After full adjustment, RRs for BDI-II ≥ 12 per 1-SD increase in peakVO$_2$ and maximum power output were 0.68 and 0.69, respectively. VO$_2$@AT was not correlated with BDI-II ≥ 12 or the BDI-II score in fully adjusted models. A comparison of regression coefficients indicated that associations of peakVO$_2$ and maximum power output with MDD, BDI-II ≥ 12, and the BDI-II sum score were stronger than corresponding associations with VO$_2$@AT. Associations for peakVO$_2$ and VO$_2$@AT were not modified by age or sex. The association between maximum power output and incident MDD was stronger in younger than older adults (*P* interaction = .029), with RRs per 1 SD at ages 35 and 65 years of 0.39 and 0.84, respectively.

Association of PA Domains With Anxiety Disorders

There were no significant relationships between the Leisure Time, Sports, and Work indices and anxiety disorders. The associations with anxiety were not modified by age or sex (Table 2).

Association of CRF With Anxiety Disorders

PeakVO$_2$, VO$_2$@AT, and maximum power output were inversely related to anxiety disorders (Table 2). After full adjustment, RRs for anxiety disorders per 1-SD increase in peakVO$_2$, VO$_2$@AT, and maximum power output were 0.69, 0.79, and 0.72, respectively. Associations were not modified by age or sex.

Table 3. Cardiorespiratory Fitness in Relation to Incident Single or Co-Occurring Depression and Anxiety[a]

	Single MDD or Anxiety OR (95% CI)	Combined MDD and Anxiety OR (95% CI)
Baecke Leisure Time Index (per SD)		
Age- and sex-adjusted	0.99 (0.90 to 1.11)	0.95 (0.78 to 1.16)
Full adjustment	1.01 (0.91 to 1.13)	0.99 (0.82 to 1.21)
P interaction with age, sex	.272, .966	.891, .897
Baecke Sports Index (per SD)		
Age- and sex-adjusted	0.96 (0.85 to 1.07)	0.87 (0.72 to 1.07)
Full adjustment	0.96 (0.85 to 1.08)	0.88 (0.72 to 1.08)
P interaction with age, sex	.483, .326	.968, .196
Baecke Work Index (per SD)		
Age- and sex-adjusted	0.94 (0.80 to 1.09)	0.99 (0.77 to 1.26)
Full adjustment	0.91 (0.78 to 1.06)	0.97 (0.75 to 1.27)
P interaction with age, sex	.120, .096	.545, .079
$PeakVO_2$ (per SD)		
Age- and sex-adjusted	0.75 (0.61 to 0.93)	0.47 (0.28 to 0.80)
Full adjustment	0.71 (0.53 to 0.94)	0.45 (0.24 to 0.84)
P interaction with age, sex	.970, .509	.443, .446
VO_2@AT (per SD)		
Age- and sex-adjusted	0.87 (0.71 to 1.07)	0.45 (0.25 to 0.81)
Full adjustment	0.92 (0.73 to 1.16)	0.62 (0.36 to 1.08)
P interaction with age, sex	.358, .888	.730, .169
Maximum power output (per SD)		
Age- and sex-adjusted	0.74 (0.61 to 0.89)	0.49 (0.32 to 0.75)
Full adjustment	0.74 (0.59 to 0.92)	0.50 (0.29 to 0.85)
P interaction with age, sex	.280, .230	.274, .300

[a]"No depression and anxiety" served as the base category for the multinomial model. Potential nonlinear relation of $peakVO_2$, VO_2@AT, and maximum power output with depression/anxiety was tested using second-degree fractional polynomials. Full adjustment included age, sex, years of schooling, alcohol consumption, smoking, and waist circumference.

Abbreviations: AT = anaerobic threshold, CI = confidence interval, MDD = major depressive disorder, OR = adjusted odds ratio from a weighted multinomial logistic regression, SD = standard deviation.

Association of CRF With Single and Co-Occurring Incident MDD and Anxiety Disorders

$PeakVO_2$ and maximum power output, but not VO_2@AT, were inversely associated with single depression or anxiety in the fully adjusted multinomial model (Table 3). $PeakVO_2$ and maximum power output but not VO_2@AT showed inverse associations with combined depression and anxiety disorder. A comparison of ORs across outcomes suggested that CRF measures were more strongly related to combined depression and anxiety than to a single diagnosis of either depression or anxiety.

DISCUSSION

In this prospective population-based cohort, we demonstrated an inverse association between self-reported habitual PA during leisure time and sports with current depressive symptoms but no relation of PA with incident or recurrent MDD. Work-related PA was not associated with MDD or depressive symptoms. Previous studies reported relationships of leisure-time PA or total PA with onset of depression.[2,4] A meta-analysis summarized the evidence from randomized controlled trials and established a modest protective effect of PA on depression (standardized mean difference [SMD] = −0.5) and a small positive effect on anxiety in nonclinical adult populations (SMD = −0.38).[4] Three cross-sectional studies[50–52] compared domain-specific PA in relation to depression. Of these, a national study of young US adults found that leisure PA was inversely related to MDD but that higher duration of work-related PA was positively associated with MDD.[51] Similar findings were found for associations of leisure-time and work-related PA with depressive symptoms in a cross-sectional, population-based study of working-age women.[50] Conversely, a population-based cross-sectional survey revealed inverse associations between leisure-time PA and depressive symptoms but not with occupational PA.[52] A large prospective study of ~30,000 Japanese workers found a *U*-shaped relation between leisure-time PA and incident depressive symptoms and a positive association between sedentary work to risk of depressive symptoms.[7] In addition, evidence suggests that PA is beneficial for the prevention and treatment of anxiety.[4,13,14,53] Several population-based studies found inverse associations between PA and incident anxiety.[1,54–57] We found no association between domain-specific PA and incident anxiety. Previous studies have not considered PA that occurs in various domains in relation to anxiety.

The present study found an inverse association between $peakVO_2$, maximum power output at peak exertion and onset of MDD, recurrent MDD, depressive symptoms, and anxiety disorders. These findings are consistent with previous studies, suggesting that low CRF predicts incidence of inpatient treatment for clinical depression[25] and elevated depressive symptoms.[20,22] The present study found no gender differences regarding the relationship between CRF and depression. The association of maximum power output and MDD was stronger in younger than in older individuals. To our knowledge, this is the first study that showed a positive association between CRF and incident anxiety. A meta-analysis quantified the available evidence from cross-sectional and prospective studies (4,039 participants) and found a modest correlation of −0.16 (95% CI, −0.21 to −0.10) between CRF and depressive symptoms, the correlation being stronger in men than in women.[24] The meta-analysis also revealed that measurement methods of CRF represent a methodological shortcoming of existing studies and recommended further studies with direct measures of CRF.[24] The present study is novel in its use of a direct assessment of CRF using $peakVO_2$, VO_2@AT, and maximum power output as gold-standard indices of CRF.[8,12,24] In addition, previous research has relied on symptom scales to assess depressive symptoms.[20,22,23] For example, several studies[20,22] used the Center of Epidemiologic Studies Depression Scale (CES-D) as measurement instrument for depressive symptoms. Unfortunately, the CES-D contains items that are directly related to fitness, including questions regarding psychomotor retardation, fatigue, weight loss, and sleep problems.[28,58–60] It seems likely that answering these questions is affected by a lack of CRF, and this would lead to differential measurement error, in which fit individuals have lower CES-D values independent of their true level

of depression.[28] The present study advances the field by using direct measures of CRF and a structured diagnostic interview, whereby measurement error in outcomes is expected to be independent and non-differential.

One possible explanation for the discrepancies of associations of PA and CRF with outcomes is that peakVO_2 is a distinct physiologic measure that is not only affected by the level of physical fitness and PA but also by the general health status, age, ethnicity, behavioral risk factors, and genetics.[8,61] Another explanation is nondifferential measurement error of PA, which might underestimate effect sizes and render associations nonsignificant.

The current study has several limitations that need to be considered when interpreting the findings. First, our study had a relatively short follow-up time, which did not permit us to investigate whether the association between PA, CRF, and depression/anxiety varies over time. Second, we used the CID-S,[36] a screening instrument, to identify cases histories of depression and anxiety at baseline. Nevertheless, because the negative predictive values of the CID-S for lifetime depression and anxiety are high (97% and 96%, respectively),[36] we are confident that we had a low chance of including false-negative cases at baseline.

Previous research has hypothesized that the relationship between PA and mental health may be complex and bidirectional[54,57] such that symptoms of depression and anxiety may also impact PA. Analyses of data from the British Whitehall II cohort illustrate the bidirectional nature of PA and mental health.[54] Inverse cross-sectional associations between PA and depression and anxiety were found. However, PA at baseline did not correlate with depression 8 years later; cumulative PA was associated with lower depressive symptoms at all time points, and cumulative exposure to depression and anxiety predicted reduced levels of PA.[54] Those findings suggest a mutually reinforcing cycle that can worsen both mental health and PA and physical fitness.[62,63]

Trauma or development of acute and chronic conditions could result in reverse causation by inducing depression or anxiety, which could lead to lower PA levels and CRF. Unmeasured risk factors (including genetic predisposition, childhood abuse, low self-esteem, and personality traits) might confound the relation between PA and mental health. Thus, although we adjusted our models for known confounding factors, unobserved and time-varying confounders pose a threat to causal inference from observational data, and future studies might consider using stronger quasi-experimental designs with multiple follow-up measurements before any causal statements regarding the associations between PA, CRF, and the development of mental disorders can be made.[62,64,65]

In conclusion, this prospective population-based study showed that domain-specific PA is inversely associated with depressive symptoms and that peakVO_2 and maximum power output are inversely associated with the risk of developing MDD or anxiety. The current study investigated the association between CRF, assessed at a single point in time, with subsequent depression and anxiety several years later, assuming that CRF remained relatively constant over time. However, CRF in adults typically decreases with age and is influenced by lifestyle.[66] Future research should examine variation in PA, CRF, depression, and anxiety over the life-course to provide further insights into the directionality of causal relationships.

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REFERENCES

1. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. *Med Sci Sports Exerc*. 2001;33(6 suppl):S587–S597, discussion 609–610.
2. Mammen G, Faulkner G. Physical activity and the prevention of depression: a systematic review of prospective studies. *Am J Prev Med*. 2013;45(5):649–657.
3. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: US Department of Health and Human Services; 2008.
4. Rebar AL, Stanton R, Geard D, et al. A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. *Health Psychol Rev*. 2015;9(3):366–378.
5. Teychenne M, Ball K, Salmon J. Physical activity and likelihood of depression in adults: a review. *Prev Med*. 2008;46(5):397–411.
6. Hanson S, Jones A. Is there evidence that walking groups have health benefits? a systematic review and meta-analysis. *Br J Sports Med*. 2015;49(11):710–715.
7. Kuwahara K, Honda T, Nakagawa T, et al. Associations of leisure-time, occupational, and commuting physical activity with risk of depressive symptoms among Japanese workers: a cohort study. *Int J Behav Nutr Phys Act*. 2015;12:119.
8. DeFina LF, Haskell WL, Willis BL, et al. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? *Prog Cardiovasc Dis*. 2015;57(4):324–329.
9. Myers J, McAuley P, Lavie CJ, et al. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57(4):306–314.
10. Barry VW, Baruth M, Beets MW, et al. Fitness vs fatness on all-cause mortality: a meta-analysis. *Prog Cardiovasc Dis*. 2014;56(4):382–390.
11. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024–2035.
12. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 9th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2013.
13. Jayakody K, Gunadasa S, Hosker C. Exercise for anxiety disorders: systematic review. *Br J Sports Med*. 2014;48(3):187–196.
14. Stonerock GL, Hoffman BM, Smith PJ, et al. Exercise as treatment for anxiety: systematic review and analysis. *Ann Behav Med*. 2015;49(4):542–556.
15. Galper DI, Trivedi MH, Barlow CE, et al. Inverse association between physical inactivity and mental health in men and women. *Med Sci Sports Exerc*. 2006;38(1):173–178.
16. Muraki S, Maehara T, Ishii K, et al. Gender difference in the relationship between physical fitness and mental health. *Ann Physiol Anthropol*. 1993;12(6):379–384.
17. Ripke S, Wray NR, Lewis CM, et al; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry*.

2013;18(4):497–511.
18. Thirlaway K, Benton D. Participation in physical activity and cardiovascular fitness have different effects on mental health and mood. *J Psychosom Res*. 1992;36(7):657–665.
19. Tolmunen T, Laukkanen JA, Hintikka J, et al. Low maximal oxygen uptake is associated with elevated depressive symptoms in middle-aged men. *Eur J Epidemiol*. 2006;21(9):701–706.
20. Becofsky KM, Sui X, Lee DC, et al. A prospective study of fitness, fatness, and depressive symptoms. *Am J Epidemiol*. 2015;181(5):311–320.
21. Dishman RK, Sui X, Church TS, et al. Decline in cardiorespiratory fitness and odds of incident depression. *Am J Prev Med*. 2012;43(4):361–368.
22. Sui X, Laditka JN, Church TS, et al. Prospective study of cardiorespiratory fitness and depressive symptoms in women and men. *J Psychiatr Res*. 2009;43(5):546–552.
23. Suija K, Timonen M, Suviola M, et al. The association between physical fitness and depressive symptoms among young adults: results of the Northern Finland 1966 birth cohort study. *BMC Public Health*. 2013;13:535.
24. Papasavvas T, Bonow RO, Alhashemi M, et al. Depression symptom severity and cardiorespiratory fitness in healthy and depressed adults: a systematic review and meta-analysis. *Sports Med*. 2016;46(2):219–230.
25. Åberg MA, Waern M, Nyberg J, et al. Cardiovascular fitness in males at age 18 and risk of serious depression in adulthood: Swedish prospective population-based study. *Br J Psychiatry*. 2012;201(5):352–359.
26. Rice MC, Katzel LI, Waldstein SR. Sex-specific associations of depressive symptoms and cardiovascular risk factors in older adults. *Aging Ment Health*. 2010;14(4):405–410.
27. Myers J, Arena R, Franklin B, et al; American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention of the Council on Clinical Cardiology, the Council on Nutrition, Physical Activity, and Metabolism, and the Council on Cardiovascular Nursing. Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association. *Circulation*. 2009;119(24):3144–3161.
28. Mukamal KJ. Invited commentary: fitness and fatness-causes of depression or of misclassification? *Am J Epidemiol*. 2015;181(5):321–324.
29. Völzke H, Alte D, Schmidt CO, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol*. 2011;40(2):294–307.
30. Wittchen H, Pfister H. *Diagnostisches Expertensystem für psychische Störungen (DIA-X)*. Frankfurt, Germany: Swets Test Services; 1997.
31. Wittchen HU, Lachner G, Wunderlich U, et al. Test-retest reliability of the computerized *DSM-IV* version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Soc Psychiatry Psychiatr Epidemiol*. 1998;33(11):568–578.
32. Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*. 1994;28(1):57–84.
33. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996.
34. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Rev Bras Psiquiatr*. 2013;35(4):416–431.
35. Aalto AM, Elovainio M, Kivimäki M, et al. The Beck Depression Inventory and General Health Questionnaire as measures of depression in the general population: a validation study using the Composite International Diagnostic Interview as the gold standard. *Psychiatry Res*. 2012;197(1–2):163–171.
36. Wittchen HU, Höfler M, Gander F, et al. Screening for mental disorders: performance of the Composite International Diagnostic-Screener (CID-S). *Int J Methods Psychiatr Res*. 1999;8(2):59–70.
37. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr*. 1982;36(5):936–942.
38. Hertogh EM, Monninkhof EM, Schouten EG, et al. Validity of the modified Baecke questionnaire: comparison with energy expenditure according to the doubly labeled water method. *Int J Behav Nutr Phys Act*. 2008;5:30.
39. Florindo AA, Latorre MdoR, Santos EC, et al. Validity and reliability of the Baecke questionnaire for the evaluation of habitual physical activity among people living with HIV/AIDS. *Cad Saude Publica*. 2006;22(3):535–541.
40. Philippaerts RM, Westerterp KR, Lefevre J. Doubly labelled water validation of three physical activity questionnaires. *Int J Sports Med*. 1999;20(5):284–289.
41. Pereira MA, FitzerGerald SJ, Gregg EW, et al. A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc*. 1997;29(6 suppl):S1–S205.
42. Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis*. 1985;131(5):700–708.
43. Koch B, Schäper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. *Eur Respir J*. 2009;33(2):389–397.
44. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702–706.
45. Beyerlein A. Quantile regression-opportunities and challenges from a user's perspective. *Am J Epidemiol*. 2014;180(3):330–331.
46. Hilbe JM. *Negative Binomial Regression*. 2nd ed. New York, NY: Cambridge University Press; 2011.
47. Buchinsky M. Quantile regression with sample selection: estimating women's return to education in the US. In: Fitzenberger B, Koenker R, Machado JAF, eds. *Economic Applications of Quantile Regression*. Heidelberg, Germany: Phsysica-Verlag; 2002:87–113.
48. Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. *J R Stat Soc Ser A Stat Soc*. 1999;162(1):71–94.
49. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22(3):278–295.
50. Kull M, Ainsaar M, Kiive E, et al. Relationship between low depressiveness and domain specific physical activity in women. *Health Care Women Int*. 2012;33(5):457–472.
51. McKercher CM, Schmidt MD, Sanderson KA, et al. Physical activity and depression in young adults. *Am J Prev Med*. 2009;36(2):161–164.
52. Teychenne M, Ball K, Salmon J. Associations between physical activity and depressive symptoms in women. *Int J Behav Nutr Phys Act*. 2008;5:27.
53. Rosenbaum S, Tiedemann A, Sherrington C, et al. Physical activity interventions for people with mental illness: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014;75(9):964–974.
54. Azevedo Da Silva M, Singh-Manoux A, Brunner EJ, et al. Bidirectional association between physical activity and symptoms of anxiety and depression: the Whitehall II study. *Eur J Epidemiol*. 2012;27(7):537–546.
55. Boschloo L, Reeuwijk KG, Schoevers RA, et al. The impact of lifestyle factors on the 2-year course of depressive and/or anxiety disorders. *J Affect Disord*. 2014;159:73–79.
56. Brunes A, Gudmundsdottir SL, Augestad LB. Gender-specific associations between leisure-time physical activity and symptoms of anxiety: the HUNT study. *Soc Psychiatry Psychiatr Epidemiol*. 2015;50(3):419–427.
57. De Moor MH, Boomsma DI, Stubbe JH, et al. Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Arch Gen Psychiatry*. 2008;65(8):897–905.
58. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol*. 1986;42(1):28–33.
59. Parikh RM, Eden DT, Price TR, et al. The sensitivity and specificity of the Center for Epidemiologic Studies Depression Scale in screening for post-stroke depression. *Int J Psychiatry Med*. 1988;18(2):169–181.
60. Thomas JL, Jones GN, Scarinci IC, et al; The Center for Epidemiologic Studies-Depression. The utility of the CES-D as a depression screening measure among low-income women attending primary care clinics. *Int J Psychiatry Med*. 2001;31(1):25–40.
61. Wilson MG, Ellison GM, Cable NT. Basic science behind the cardiovascular benefits of exercise. *Heart*. 2015;101(10):758–765.
62. de Jonge P, Roest AM. Depression and cardiovascular disease: the end of simple models. *Br J Psychiatry*. 2012;201(5):337–338.
63. Elderon L, Whooley MA. Depression and cardiovascular disease. *Prog Cardiovasc Dis*. 2013;55(6):511–523.
64. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet*. 2014;23(R1):R89–R98.
65. Hernán MA, Robins JM. *Causal Inference*. Boca Raton, FL: CRC; 2011.
66. Jackson AS, Sui X, Hébert JR, et al. Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. *Arch Intern Med*. 2009;169(19):1781–1787.