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Research paper

The association between cardio-respiratory fitness and incident depression: The Maastricht Study

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ABSTRACT

Background: Moderate to vigorous physical activity (MVPA) can help to prevent depression, but identification of the most important psycho-biological pathways involved is unclear. The improvement of cardio-respiratory fitness (CRF) in response to MVPA can vary markedly, we therefore examined the association between CRF and the incidence of depressive symptoms.

Methods: We used data from The Maastricht Study, a large population-based prospective-cohort study. CRF was estimated at baseline from a graded submaximal exercise protocol and MVPA was measured with accelerometry. Depressive symptoms were assessed using the validated Dutch version of the 9-item Patient Health Questionnaire, both at baseline and during annual follow-up over five years. Cox proportional hazards models were used.

Results: A total of 1,730 individuals without depressive symptoms at baseline were included in the analysis. During the 5-year follow-up, n = 166 (9.6%) of individuals developed depressive symptoms. Compared to individuals with a low CRF, those with a moderate-to-high CRF had a significantly lower risk of developing depressive symptoms, independent of MVPA (medium CRF: HR = 0.49 (95%CI = 0.33–0.72); high CRF: HR = 0.48 (95% CI = 0.30–0.75). These associations were adjusted for age, sex, level of education, diabetes status, smoking status, alcohol use, energy intake, waist circumferences and antidepressant medications.

Limitations: PHQ-9 is a validated screening instrument, but it is not a diagnostic tool of depression.

Conclusions: Higher CRF was strongly associated with a lower risk of incident depressive symptoms over 5-year follow-up, independent of the level of MVPA at baseline, suggesting that interventions aimed at improving CRF could reduce the risk of depression.

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1. Introduction

Depression represents a significant contributor to the global burden of disease and affects more than 300 million people in all communities across the world (Lepine and Briley, 2011). One in five people experience a period of depression in their lives, and it is the leading cause of disability worldwide (World Health Organization, 2017). Depression is accompanied by behavioural and biological features that are deleterious for physical health, especially in the cardiovascular system (Goldstein et al., 2015). It has been estimated that individuals with depression die, on average, about ten years earlier than those who are not depressed, even when excluding deaths by suicide (Walker et al., 2015). Given this high burden of depression, it is important to identify risk factors of depression that could inform preventive strategies to reduce depression.

Cardiorespiratory fitness (CRF) is an important component of physical fitness that reflects the capacity of lungs, heart, vascular system, and exercising muscles in transporting and using nutrients and oxygen. Moderate to vigorous physical activity (MVPA), such as body mass index (BMI), smoking habits, comorbidities and genetic factors are known to influence or modulate CRF (Bouchard and Rankinen, 2001). Low CRF has been associated with a higher risk of metabolic syndrome, cardiovascular disease, and premature mortality (Kaminsky et al., 2019). A recent review shows that a low CRF is also associated with greater risk of common mental health disorders (Kandola et al., 2019); in both cross-sectional and longitudinal studies a low level of CRF was associated with higher risk of depression (Kandola et al., 2019; Willis et al., 2018). However, longitudinal studies on the association between CRF and risk of depression are currently scarce.

CRF is a stronger health risk factor and better predictor of morbidity and mortality than PA levels (Kaminsky et al., 2019). The cardio-metabolic effects of MVPA can vary between individuals with ultimately differential effects on CRF; and consequently, on morbidity and mortality, which could better explain the stronger association of CRF than MVPA with health outcomes. MVPA can have a large impact on cardiovascular risk factors such as body weight, glycemia, insulin resistance, endothelial function and low-grade inflammation (Reiner et al., 2013), several of these factors have also been implicated in the development of depression. We hypothesize that these cardio-metabolic factors mediate, at least in part, the beneficial effects of PA on both depression and CRF and that CRF might be viewed as an indicator of the potential beneficial neurobiological effects of long-term MVPA.

Previous observational studies on CRF and depression have not taken MVPA into account in the analyses. The aim of this study was to examine the association between CRF and the incidence of clinically relevant depressive symptoms in a large population-based cohort study: The Maastricht Study. Our hypothesis was that a higher CRF is associated with lower risk of incident clinically relevant depressive symptoms and that this predictive value is independent of the current level of MVPA as well as other major confounding factors such as waist circumference and co-morbidities (diabetes, mobility limitation, CVD, and antidepressant medications use).

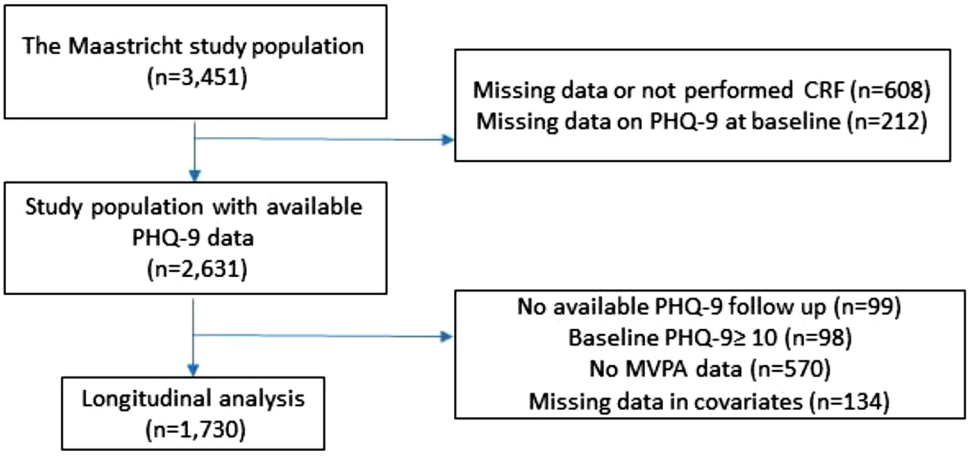
2. Methods

2.1. Study population and design

We used data from The Maastricht Study, a population-based observational prospective cohort study. A detailed rationale and methodology were published elsewhere (Schram et al., 2014). In brief, the study focuses on the etiology, pathophysiology, complications and co-morbidities of type 2 diabetes mellitus (T2DM) and is characterized by an extensive phenotyping approach.

Eligible individuals were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Individuals were recruited through mass media campaigns, from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficacy. The present study includes longitudinal data from the first 3451 individuals, who completed the baseline survey between November 2010 and September 2013. Full data on CRF, depressive symptoms, accelerometer measures and covariates were available in $n = 1730$. The main reasons for missing data were: CRF test not performed ($n = 425$) or invalid data ($n = 183$), missing measurements of depressive symptoms at baseline ($n = 212$) or during follow-up ($n = 99$), missing or invalid accelerometry data ($n = 570$), and missing data in covariates ($n = 134$).The relatively large number of missing data on MVPA was because the activPAL measurement started approximately 1 year after the start of the study.

Since the aim of the current study was to assess the incident depression, individuals with depressive symptoms at baseline ($n = 98$) were excluded from the analysis (Fig. 1). Follow up data on depressive symptoms by questionnaire were collected annually after the baseline examination. Institutional Medical Ethical Committee (NL31329.068.10)



PHQ-9, 9-item Patient Health Questionnaire. Missing data on MVPA were mainly due to logistic reasons.

Fig. 1. flowchart on the derivation of the study sample used in the current analysis. PHQ-9, 9-item Patient Health Questionnaire.

and Ministry of Health, Welfare and Sports of the Netherlands (Permit 131,088–105,234-PG) ethically approved the study. Written informed consent was required to all individuals.

2.2. Measures

2.2.1. Cardiorespiratory fitness

As an objective measure of CRF estimated maximum power output adjusted for body mass (Wmax kg^{-1}) was used. Wmax was estimated from a graded submaximal exercise protocol performed on a cycle ergometer system (CASETM version 6.6 in combination with e-bike; GE Healthcare, Milwaukee, WI). For safety reasons, individuals with recent or manifest cardiovascular complications were excluded from the exercise test. The submaximal exercise test has been described in more detail before (Van Der Velde et al., 2017). In brief, Wmax was calculated from HR values if the test was completed based on heart rateor based onRating of Perceived Exertion (RPE)measured with the Borg scale. The exercise protocol was considered as "completed" when heart rate reached ≥85% of the estimated maximum (HRmax, 220-age) or when the RPE was scored as ≥17 by the individual. If heart rate < 85% or RPE < 17 by the end of stage 7 which was the maximum (work load of 175 W), the test was also stopped. The test could also be prematurely aborted on medical grounds or when the individual was unwilling to continue. Wmax from uncompleted tests was calculated from HR if ≥75% of HRmax was achieved and Wmax was calculated from RPE values if an RPE ≥ 15 was scored (Van Der Velde et al., 2017). Submaximal values of heart rate and RPE with workload from each stage were extrapolated to 100% of maximum heart rate or an RPE of 20 and corresponding workload (Wmax) using individual linear regression models. More details on the methodology used are reported elsewhere (Van Der Velde et al., 2017).

In this study CRF (Wmax kg-1) has been used as a continuous variable and was categorized into tertiles (low, medium, and high fit) based on sex and age (40–49, 50–59, 60–69, and >70 year) (Van Der Velde et al., 2017). The CRF was only assessed at baseline.

2.2.2. Depression

Depressive symptoms were assessed using the validated Dutch version of the 9-item Patient Health Questionnaire (PHQ-9) both at baseline and during annual follow-ups over five years (Kroenke et al., 2001). The PHQ-9 is a multipurpose self-administered instrument for screening, diagnosing, monitoring and measuring the severity of depression. The PHQ-9 incorporates the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) criteria with other leading major depressive symptoms into a brief self-report tool (American Psychiatric Association, 2013). It rates the frequency of the symptoms which factors into the scoring severity index. The PHQ-9 is brief and useful in clinical practice and it is completed by the patient in minutes and rapidly scored by the clinician. The PHQ-9 measures both cognitive (thoughts about oneself and problems of the mind), and somatic symptoms of depression (various bodily sensations that a depressed individual perceives as unpleasant or worrisome) (Smolderen et al., 2009). It comprises nine items rated on a four-point scale, ranging from 0 = "not at all" to 3 = "nearly every day". Response options are used to calculate a continuous total-score ranging from 0 (no symptoms) to 27 (all symptoms present nearly every day). When one or two items were missing, the total-score was calculated as 9 × (total points/9 − number of missing items) and rounded to the nearest integer. Based on previous studies, a pre-defined cut-off score of ≥10 was used as a dichotomous scoring system for defining clinically relevant depressive symptoms (Pettersson et al., 2015). Incident depressive symptoms wereassessed by use of the PHQ-9 questionnaire annually during follow up.Incident depressive symptoms were defined as no depressive symptoms at baseline (PHQ-9 ≤ 10) and presence of clinically relevant depressive symptoms on at least one follow-up moment (PHQ-9 ≥ 10). The Mini-International Neuropsychiatric Interview (MINI) was used at baseline to assess lifetime history of Major Depressive Disorder (MDD) by asking about presence of symptoms during minimally two weeks in lifetime (Sheehan et al., 1998).

2.2.3. Covariates

The following variables were considered as potential confounders a priori: age, sex, educational level, diabetes status, smoking status, alcohol use, energy intake, waist circumference, antidepressant medication use, MVPA, mobility limitations, and a history of cardiovascular disease (CVD). Questionnaires were used to collect information on age (in years), sex, educational level, smoking status, alcohol consumption, energy intake, mobility limitations and CVD history. Educational level was divided into low, middle, and high. Smoking status was divided into current, former, and never smokers. Alcohol consumption was divided, into three categories: non-consumers, low consumers (for women ≤7 glasses alcohol per week; for men ≤14 glasses alcohol per week), and high consumers (for women >7 glasses per week; for men >14 glasses alcohol per week). Energy intake was derived from a food frequency questionnaire, which was developed for The Maastricht Study (van Dongen et al., 2019), and calculated as the mean energy intake per day (kcal). Mobility limitation was acquired from the Dutch version of the Short Form Health Survey and was defined as having difficulty with stair climbing and/or walking 500 m. CVD history was derived from the Rose questionnaire and defined as a self-reported history of any of the following conditions: myocardial infarction, cerebrovascular infarction or hemorrhage, percutaneous artery angioplasty of, or vascular surgery on, the coronary, abdominal, peripheral, or carotid arteries. Medication use was assessed during a medical interview where generic name, dose, and frequency were registered. During physical examination waist circumference was measured (Schram et al., 2014). To determine diabetes status, all individuals underwent a standardized seven-point oral glucose tolerance test as described elsewhere (World Health Organization, 2006). Glucose metabolism was defined according to the World Health Organization 2006 criteria and individuals were categorized as having a normal glucose metabolism (fasting plasma glucose < 110.0 mg/dL), prediabetes (fasting plasma glucose 110.0–125.0 mg/dL), T2DM (fasting plasma glucose ≥ 126.0 mg/dL), or type 1 (and other types). Individuals on diabetes medication and without type 1 diabetes were also considered as having T2DM (World Health Organization, 2006). PA was measured using the activPAL3™ physical activity monitor, (PAL Technologies, Glasgow, UK) (van der Berg et al., 2016). MVPA was defined as stepping time with a step frequency ≥100 steps/minute (Tudor-Locke et al., 2011).

2.2.4. Statistical analysis

Descriptive statistics are presented for the total population and stratified by level of CRF (Lowest, medium, highest). To assess the differences between individuals, we performed chi-square test for categorial variables, and analysis of variance (ANOVA) for continuous variables. Cox proportional hazards models were used to examine the association between CRF and incident depressive symptoms, yielding Hazard Ratios (HR) and 95% Confidence Intervals (95% CIs). Cox proportional hazard assumptions have been checked by visually inspecting the Kaplan-Meier curves and were not violated. In the survival analysis, incident depressive symptoms were treated as the failure event. Time at risk in days was calculated from the study entry until study exit – the latter being date of depression event, or date of becoming lost to follow-up or study end - whichever came first. Considering the oversampling of T2DM participants, Model 1 was firstly adjusted for age, sex, level of education, and diabetes status. In Model 2 we additionally adjusted for lifestyle risk factors as smoking status, alcohol use, energy intake, waist circumference, and for the use of antidepressant medication. In Model 3, we separately and additionally adjusted for MVPA; lastly in Model 4 comorbidities as mobility limitation, and history of CVD were also added. Covariates used in the adjusted models were chosen a priori based on literature. In addition,

we performed several sensitivity analyses. First, individuals who used antidepressant medication at baseline were excluded (n = 80). Second, individuals with a lifetime history MDD were excluded (n = 544); and third, individuals with mobility limitation were excluded (n = 270). In addition, we tested interaction between CRF and sex and CRF and diabetes status (considering both CRF as categorical and as a continuous variable). Lastly, a strict analysis excluding individuals with any missing PHQ-9 data over five follow-up years and allowing only one missing PHQ-9 assessment over five years of follow-up were conducted as well. We additionally compared baseline characteristics of the included study population with the excluded participant (n = 1721). Moreover, we also compared baseline characteristics of those with complete follow-up data to those with one or more missing follow-up measurement. All analyses were performed using IBM SPSS software version 21.0 (IBM Corp. Armonk, NY, USA). Associations with $p < 0.05$ were considered statistically significant in two-sided tests.

3. Results

Table 1 presents the population characteristics (n = 1730) stratified by level of CRF. The study population, of which 50.8% were women, had a mean ± standard deviation (SD) age of 59.9 ± 8.0 years. One hundred and sixty-six (9.6%) individuals developed clinically relevant depressive symptoms (PHQ-9 ≥ 10) during the 7958 person-years, with an incidence rate of 20.9 cases per 1000 person-years. On average, participants with low level of CRF had a lower level of education, were more often current smokers, had alower alcohol intake, more often had T2DM, had a larger waist circumference, had lower levels of MVPA, and higher depressive symptoms score at baseline (Table 1). Comparing baseline characteristics of the included study population with the excluded participant (n = 1721), the excluded participants were more often men, had a lower level of education, were more often smokers, had a larger waist circumference, had lower levels of MVPA, and a higher mean score on baseline depressive symptoms, and a lower CRF (Supplementary 1). While, the participants with one or more missing follow-up measurement were more often smokers, had lower levels of MVPA and a lower CRF compared to participants with complete follow-up. The two groups did not statistically differ in sex, level of education, waist circumference, and baseline depressive symptoms.

An inverse association between CRF – considered both as continuous and categorical measurement – and incident depressive symptoms was found in all the models (Table 2). Compared to people with a low CRF, those with a medium or high CRF had a significantly lower risk of developing clinically relevant depressive symptoms (Model 2, medium CRF: HR = 0.50 (95% CI = 0.34–0.74); high CRF: HR = 0.51 (95% CI = 0.33–0.79). Interestingly, the strength of the association was not attenuated after further adjustment for MVPA (Model 3) and for mobility limitation, and history of CVD (Model 4).

In order to minimize selection bias and to confirm the robustness of the findings, several sensitivity analyses have been performed with different in- and exclusion criteria of the subjects (Table 3). In sensitivity analysis 1, we first excluded individuals who used antidepressant medications at baseline. Results remained essentially the same, compared to people with a low CRF, those with a medium (HR = 0.48 (95% CI = 0.31–0.7) or high CRF (HR = 0.55 (95% CI = 0.34–0.87) had a significantly lower risk of clinically relevant depressive symptoms. In sensitivity analysis 2, after removing individuals with a lifetime history of MDD (sample size n = 1186 subjects), those with a high CRF had a significantly lower risk of depression HR = 0.42 (95% CI = 0.22–0.83) compared to those with low CRF. In sensitivity analysis 3, after excluding those with mobility limitation (sample size n = 1460 subjects), the association was attenuated but remained significant comparing the low CRF (reference) with the medium CRF, HR = 0.54 (95% CI = 0.33–0.89), while, it was non-significant but directionally congruent with previous results when the low CRF was compared with the high HR = 0.59 (95% CI = 0.35–1.00). Lastly, we performed analysis restricted to individuals without missing PHQ-9 follow-up over five years (n = 1164) of assessment and another analysis allowing only one missing PHQ-9 assessment (n = 1442) (Supplementary 2). In these analyses, too, results were similar to the main results, both when CRF was considered as a continuous and as a categorical measurement.

In summary, all the sensitivity analysis provided further support for the robustness of our results. Interactions between CRF and sex and CRF and diabetes status were tested and were not statistically significant ($p > 0.10$).

Table 1
Descriptive characteristics of the study population (n = 1730), stratified by tertiles of CRF.

Characteristic	Lowest	Medium	Highest	P-value
Total population, n(%)	525 (30.4)	601 (34.7)	604 (34.9)	
Age (years), mean ± SD	60.44 ± 8.1	59.82 ± 7.9	59.53 ± 7.9	0.150
Sex (women), n(%)	250 (47.6)	311 (51.7)	318 (52.6)	0.205
Educational level, n(%)				
low	219 (41.7)	168 (28.0)	138 (22.8)	0.000
medium	148 (28.2)	185 (30.8)	155 (25.7)	
high(%)	158 (30.1)	248 (41.3)	311 (51.5)	
Smoking, n(%)				
never	161 (30.7)	233 (38.8)	259 (42.9)	0.000
former	287 (54.7)	311 (51.7)	289 (47.8)	
current	77 (14.7)	57 (9.5)	56 (9.3)	
Alcohol use, n(%)				
none	104 (19.8)	84 (14.0)	81 (13.4)	0.007
low	301 (57.3)	357 (59.4)	344 (57.0)	
High	120 (22.9)	160 (26.6)	179 (29.6)	
Waist circumference (cm), mean ± SD	101.71 ± 13.8	93.61 ± 10.9	88.00 ± 9.9	0.000
Diabetes status, n(%)				
no diabetes	308 (58.7)	479 (79.7)	544 (90.1)	0.000
T2DM	217 (41.3)	122 (20.3)	60 (9.9)	
Depressive symptoms, mean ± SD	3.24 ± 3.7	2.13 ± 2.7	2.15 ± 2.6	0.000
Antidepressant medications (yes), n(%)	37 (7.0)	24 (4.0)	19 (3.1)	0.005
Major Depressive Disorder (MINI) (yes), n(%)	14 (2.8)	5 (0.9)	3 (0.5)	0.002
Lifetime Depressive Disorder (MINI) (yes), n(%)	164 (34.0)	141 (24.7)	135 (23.6)	0.000
Prior CVD (yes), n(%)	90 (17.1)	77 (12.8)	66 (10.9)	0.008
Mobility limitation (yes), n(%)	152 (29.0)	77 (12.8)	41 (6.8)	0.000
Energy intake (Kcal), mean ± SD	2097.0 ± 586.4	2192.2 ± 579.2	2183.4 ± 581.9	0.011
MVPA (min/day), mean ± SD	44.89 ± 21.8	56.29 ± 24.3	67.13 ± 28.3	0.000
CRF (Wmax/kg), mean ± SD	1.58 ± 0.3	2.12 ± 0.3	2.71 ± 0.4	0.000

Table 2
Association between CRF and incident depressive symptoms over five years of follow-up.

	Incident rate per 1000 person years	Model 1			Model 2			Model 3			Model 4		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
CRF(W_{max})	20.9	0.44	0.32–0.62	0.000	0.54	0.37–0.79	0.001	0.50	0.34–0.74	0.001	0.56	0.38–0.83	0.004
CRF tertils													
Lowest	10.81	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
Medium	5.28	0.45	0.31–0.65	0.000	0.50	0.34–0.74	0.001	0.49	0.33–0.72	0.000	0.52	0.35–0.78	0.001
Highest	4.78	0.42	0.28–0.63	0.000	0.51	0.33–0.79	0.006	0.48	0.30–0.75	0.001	0.52	0.33–0.83	0.006

Model 1: adjusted for age, sex, level of education, and diabetes status.
Model 2: additionally adjusted for smoking status, alcohol use, energy intake, waist circumference and antidepressant medications.
Model 3: additionally adjusted for MVPA.
Model 4: additionally adjusted for mobility limitation, and CVD.

Table 3
Association between CRF and incident depressive symptoms over five years of follow-up in subjects a) without antidepressant medications use; b) without lifetime history of major depression; and c) without mobility limitation.

	Model 4	Incident rate per 1000 person years	a) without antidepressant medications* (n = 1650)			Incident rate per 1000 person years	b) without lifetime history MDD* (n = 1186)			Incident rate per 1000 person years	c) without mobility limitation* (n = 1460)		
	HR (95% CI)		HR	95% CI	p-value		HR	95% CI	p-value		HR	95% CI	p-value
CRF (W_{max})	0.56 (0.38–0.83)	18.49	0.54	0.36–0.82	0.003	12.82	0.43	0.25–0.75	0.003	14.84	0.55	0.38–0.88	0.013
CRF tertils													
Lowest	(Ref)	9.25	(Ref)			5.27	(Ref)			5.85	(Ref)		
Medium	0.52 (0.35–0.78)	4.56	0.48	0.31–0.73	0.001	4.57	0.67	0.38–1.17	0.158	4.28	0.54	0.33–0.89	0.016
Highest	0.52 (0.33–0.83)	4.69	0.55	0.34–0.87	0.011	2.99	0.42	0.22–0.83	0.012	4.71	0.59	0.35–1.00	0.052

Model 4 adjusted for age, sex, level of education, diabetes status, smoking status, alcohol use, energy intake, waist circumferences, antidepressant medications, MVPA, mobility limitation, and CVD.
* Adjusted for age, sex, level of education, and diabetes status, smoking status, alcohol use, energy intake, waist circumferences and antidepressant medications.

4. Discussion

We evaluated the longitudinal association between CRF and risk of clinically relevant depressive symptoms in middle aged and older individuals living in the community. A higher CRF was associated with a lower risk of incident clinically relevant depressive symptoms over five years, independent of the current level of MVPA. Compared to a low CRF, participants with moderate-to-high CRF had an approximately 50% reduced risk of developing depressive symptoms during follow-up.

Previous studies reported an inverse association between a higher level of CRF and incident clinically relevant depressive symptoms, with a 20–50% lower risk of depression (Baumeister et al., 2017; Schuch et al., 2016; Shigdel et al., 2019; Willis et al., 2018). This relatively large variation in observed risk reduction may be due to methodological differences between the studies such as, length of follow-up, sample size, different potential confounders considered, or methods used to measure CRF. A maximal treadmill test and models for non-exercise estimation of CRF were used by Shigdel et al. (Shigdel et al., 2019), whilst time to maximum effort trough the modified Balke protocol was used by Willis et al. (Willis et al., 2018). The length of follow-up ranged between 1 to more than 10 years (Schuch et al., 2016).

In our study, we separately adjusted for current participation in MVPA which did not alter the strong association between CRF and the risk of depressive symptoms. CRF can be considered a measure of lifetime PA exposure and the intensity of these activities, both are intrinsically interrelated with complementary benefits. However, this beneficial long-term effect of MVPA on physical health status and CRF can vary markedly between individuals and is modulated by factors such genetics, smoking habits, BMI, cardiopulmonary function, age, sex, heart rate, and co-morbidities (particularly previous CVD) (Stensvold et al., 2017). In other words, long-term MVPA-based interventions or other approaches that lead to increase MVPA may be effective in preventing depression so far as they also lead to an improvement in CRF. Short-term MVPA or low-intensity PA may not be sufficient to prevent clinically relevant depressive symptoms. Moreover, in those individuals in whom MVPA seems to have little effect on their CRF more exercise might not be an efficient approach to reduce the risk of depression. As we adjusted our analyses for several confounding factors (as for instance smoking, BMI, and cardiovascular disease), others as genetic and/or early life factors might determine the efficacy of MVPA to improve CRF, reducing, in turn, the risk of depression.

Multiple pathways are probably involved in the long-term effect of MVPA on the risk of depression in these individuals, such as reducing/managing weight, improving sleep quality and duration as well as beneficial adaptations in homeostatic systems involved in the response to stress (Rimmele et al., 2007). In in-vivo models, PA increased the level of both noradrenalin and serotonin, imitating the serotoninergic effect of some antidepressant medications (Meeusen and De Meirleir, 1995). Moreover, PA has a beneficial effect in hypothalamic-pituitary-adrenal axis regulation and dampens inflammatory processes, both systems have been implicated in the development of depression (Rimmele et al., 2007). Additionally, higher levels of brain derived neurotrophic factor have been found after PA (Szuhany et al., 2015). Furthermore, PA can also have beneficial effects on (micro)vascular dysfunction which has been associated with the risk of depression during the later phases of life (van Agtmaal et al., 2017). Impaired vascular autoregulation of the brain vasculature may result in relative under-perfusion in areas involved in mood regulation, due to an uncoupling of regional cerebral blood flow with regional metabolic activity which may impair cognitive and affective processes (Taylor et al., 2013). The strong association of CRF, which reflects the maximal capacity of transport and uptake of nutrients and oxygen, with incident

depression is in line with this vascular hypothesis of depression. In order to better define the role of PA in preventing depression, further intervention studies are needed to determine which common pathways are involved in the improvement in CRF and mood regulation.

5. Strengths and limitations

The main strength of this study is its being a large population-based longitudinal study with a mean 5-year follow up. Moreover, analyses were adjusted for a large range for potential confounders including alcohol use, smoking status, waist circumference, energy intake, antidepressant medication use, mobility limitations, and history of CVD. Besides, sensitivity analyses confirmed the robustness of the results, since the association did not change after controlling for several factors and after applying more strict selection criteria (excluding subjects with antidepressant medications use; lifetime history of major depression; and with mobility limitation). Moreover, interactions between CRF and sex and CRF and diabetes status were tested and were not statistically significant ($p > 0.10$).

Another strength is the objectively measured MVPA at baseline with 24-hr continuous accelerometry during 8 days, and CRF was derived form a sub-maximal bicycle exercise protocol using both heart rate and rating of perceived exertion, which is a valid method for estimation of CRF (Coquart et al., 2014). One of the limitations of (sub)maximal exercise testing is that these protocols are based upon reaching a specific heart rate, but some individuals cannot reach this heart rate, e.g. because of the use of beta-blockers. By also measuring the rate of perceived exertion, the number of participants whose results would otherwise be excluded can be reduced.

The use of the PHQ-9 questionnaire in order to detect incident depression has limitations. The PHQ-9 questionnaire is a validated screening instrument to measure depressive symptoms, suggestive of depression, but it is not a diagnostic tool of major depressive disorder. However, as the PHQ-9 has a high sensitivity and specificity compared to the psychiatric interview, the misclassification of depression is expected to be low (Levis et al., 2019). Also, because the nature of the study, depressed participants or participants with more severe symptoms were probably less prone to participate and this might have resulted in selection bias. Moreover, participants with recent or manifest cardiovascular complications were excluded from the exercise test. These exclusions might have affected the strength of the association found in our analysis, possibly resulting in an underestimation. Lastly, the study population is mainly Caucasian and so generalizability to other ethnicities should be performed with caution.

6. Conclusions

Results of our prospective population-based cohort study show that a higher CRF was strongly associated with a lower risk of incident, clinically relevant, depressive symptoms over time. This lower risk was independent of MVPA at baseline. Improvement of cardio-respiratory fitness by PA can vary markedly between individuals. Therefore, further knowledge into understanding which factors could improve CRF especially in the non-responders and its association with incident depression is needed to further improve the efficacy of PA programs to reduce the high burden of depression in our society.

Ethical standard

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 200.

Contributors

Authors VG, AK, NS designed the study; VG analysed the data. Authors VG wrote the first version of the manuscript. All authors read and critically revised the paper. All Authors approved the final version of the manuscript.

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Declaration of Competing Interest

None to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.09.090.

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