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Cardiorespiratory fitness in midlife and subsequent incident depression, long-term sickness absence, and disability pension due to depression in 330,247 men and women

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ABSTRACT

Objective: Specific information for whom and when cardiorespiratory fitness (CRF) is associated with depression risk is lacking. We aimed to study the association between adulthood CRF and incident depression, long-term sickness absence, and disability pension due to depression, as well as examine moderation of sex, age, education, and occupation on associations.

Methods: A large prospective cohort study follows participants over time with Swedish occupational health screenings data. The study includes 330,247 individuals (aged 16–79 years, 46% women) without a depression diagnosis at baseline. CRF was estimated from a submaximal cycle test.

Results: CRF was associated beneficially from low to higher levels with incident depression and long-term sickness absence due to depression. Further, CRF at high levels (≥46 ml/min/kg) was associated with a decreased risk of receiving disability pension due to depression. The associations remained after adjustment for age and sex, but not lifestyle-related factors and co-morbidity. Participants with moderate and high CRF had 16% and 21%, respectively, lower risk for incident depression, and participants with high CRF had 11% lower risk for long-term sickness absence due to depression. Associations between higher CRF and the outcomes were mainly evident in men, younger participants, and individuals with low education.

Conclusion: In a large sample of adults without a depression diagnosis at baseline, higher CRF was shown to be beneficially related to the risk of incident depression and, to some extent, long-term sickness absence due to depression. If causal, targeted interventions focusing on increasing CRF in these sub-groups should be prioritized.

1. Introduction

Depression is the leading cause of disability worldwide (Santomauro et al., 2021) and is expected to increase until 2030 (World Health Organization, 2022). However, the knowledge of factors possibly delaying or reducing development remains unclear. Modifiable lifestyle factors are particularly interesting, as they may be directly amenable to interventions. Cardiorespiratory fitness (CRF) is one such modifiable lifestyle-related factor, which depends on the current level of moderate-to-vigorous intensity physical activity with a substantial genetic contribution of 44–68% (Miyamoto-Mikami et al., 2018). CRF has been linked to risk of depression in both clinical and healthy population samples (Kandola et al., 2019; Schuch et al., 2016b). Improvements in CRF have been suggested to predict a greater reduction in depression severity among individuals who were clinically depressed (Rahman et al., 2018), and CRF in early adulthood has been strongly associated with chronic disability due to psychiatric causes later in life (Henriksson et al., 2019).

Depression incidence and prevalence vary in different sub-groups, such as between sexes, age groups, and socioeconomic levels (Salk et al., 2017; Kessler and Bromet, 2013). More specific information on for whom and when CRF may be associated with depression is lacking and has been called for. Examining moderation factors may help understand the mechanisms between CRF and depression. This can be helpful in both clinical practice and interventions (Etnier J, 2012).

Moreover, a large part of sickness absence and disability pension in

Abbreviations: CRF, Cardiorespiratory fitness; HPA, Health profile assessment; BMI, Body mass index.

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Sweden is due to mental ill-health, including depression (Swedish Social Insurance Agency, 2023). However, to the best of our knowledge, there is no available study on the association between mid-life CRF and sickness absence or disability pension due to depression in men and women.

The present study will contribute with new knowledge on if, and to what extent CRF can be used as a marker for risk of future depression and related consequences. We will be able to conduct moderation analyses to examine if the associations between differ in magnitude across different sub-groups.

The overall aim of this study was: firstly, to study the association between adulthood CRF and a) incident depression, b) long-term sickness absence due to depression, and c) receiving disability pension due to depression in individuals with no diagnosis of depression at baseline. Secondly, to examine if sex, age, educational level, and occupation moderate any longitudinal associations between CRF and the outcomes.

2. Method

This large-scale prospective observational cohort study used combined exposure data from the Health Profile Assessment (HPA) database and outcome data from Swedish national registers to follow individuals over time. HPAs have been carried out in Swedish health services since the 1970s, and data have been stored in a central database since 1990 (earlier tests manually recorded into the database). Participation is optional and free of charge for the individual and offered to all employees working for a company/organization connected to occupational or other health services. An HPA comprises a questionnaire on physical activity and lifestyle habits, a physical examination including anthropometrics and estimated maximal oxygen consumption (VO_2max) from a submaximal ergometer cycle test, and an in-depth interview with a HPA coach. The HPA database is managed by the HPI Health Profile Institute (Stockholm, Sweden), which is responsible for standardizing methods, education of HPA coaches, and developing software for data collection.

From October 1982 until December 2020, data from a total of 336,557 men and women with a first-time HPA, a valid estimate of CRF, and data for all main co-variates (sex, age, educational, exercise habits, smoking, BMI, and co-morbidity) were included in the analyses. The mean year of inclusion was 2010 (SD 5.6, range: 1982–2020). Out of these, a total of 6310 were excluded due to a previous incident depression diagnosis, according to the Swedish national patient registry. Hence, 330,247 were included in the analyses (Supplement Fig. A.1). The participants gave written informed consent at the HPA to participate and that their information was saved in the database. The study was approved by the Stockholm Ethics Review Board (Dnr 2015/1864–31/2, 2016/9–32, and 2019–05711) and adhered to the Declaration of Helsinki.

2.1. Assessment of cardiorespiratory fitness

CRF was assessed by the standardized submaximal Åstrand cycle ergometer test (Astrand, 1960). VO_2max was estimated based on the heart rate response to six minutes of cycling on one individually chosen work rate (≈13 on Borg's perceived exertion scale). To minimize well-known errors with submaximal testing, participants were requested to refrain from vigorous activity the day before the test, not consume a heavy meal for three hours, smoke/snuff for one hour, and avoid stress before the test. Previous validation studies have shown small and non-significant mean differences on group level [−0·07 l/min, 95% confidence interval (CI) −0·21 to 0·06] between estimated VO_2max using the Åstrand test and direct measured VO_2max during maximal effort on treadmill, with an absolute error and coefficient of variance similar to other submaximal tests (Standard error of estimate = 0·48 l/min, coefficient of variation = 18·1%) (Bjorkman et al., 2016). In the analyses, CRF was used as a continuous variable as well as categorized into four groups using arbitrary, a priori, cut-offs: Very low CRF ≤ 25, Low CRF > 25–32, Moderate CRF > 32–46, and High CRF > 46 ml/min/kg. These cut-offs have been used previously and are described in more detail (Ekblom-Bak et al., 2021).

2.2. Assessments of outcomes

Outcome data were retrieved from national registries and linked to the HPA database individually using the unique Swedish personal identity number. The Swedish national patient registry was used to retrieve data on incident depression (ICD10 codes F32–34, and F38), and the national cause of death registry was used to attain information on individuals who had died during follow-up. Long-term sickness absence (>14 days, definition according to the Swedish Social Insurance Agency) and disability pension due to depression on at least 25% of full-time work were retrieved from the Swedish Social Insurance Agency using the same ICD10 codes as for incident depression. All participants were followed from their HPA to the first event for each outcome, to their death, or until 2019-12-31 for incident depression, 2020-06-30 for long-term sickness absence, and 2020-11-30 for disability pension.

2.3. Assessments of covariates and moderators

Exercise habits, smoking, overall health, use of mood-stabilizing medication, insomnia, and loneliness were all self-reported through the questionnaire (see Supplement Text 1). Body mass was assessed with a calibrated scale in light-weight clothing to the nearest 0·5 kg. Body height was assessed using a wall-mounted stadiometer to the nearest 0·5 cm. Body mass index (BMI) was subsequently calculated. Somatic and/or psychiatric co-morbidity was ascertained using the Swedish national patient registry as the presence of any incident case of either Heart disease (ICD10 code: I00-I99), Cancer (C00-D48), Other psychiatric disorders (F00-F09, F20–31, F39), and/or Musculoskeletal conditions (M00-M25, M40-M99) prior or after the HPA. The highest educational attainment at the time for the HPA was obtained from Statistics Sweden and defined as length of education (<9 years to postgraduate education). Occupational group was assessed using the Swedish Standard Classification of Occupations-codes (SSYK), using the first figure of the four-digit SSYK-code to define nine major groups. These were further categorized into white-collar and blue-collar occupational groups.

2.4. Statistical analysis

The association between the three outcomes and CRF were analyzed using Cox regression models (obtaining hazard ratios (HRs) with 95% CIs with natural cubic splines). Knots were set at 25, 32, and 46 ml/min/kg to match the cut-offs used for the analyses of CRF categories. Reference levels were set at 22 ml/min/kg, representing the mean estimated VO_2max among participants below the lowest knot. Covariates for the multivariable-adjusted models were chosen according to a pre-specified working model (Supplement Fig. B.1.); sex (male/female), age (continuous) (Model 2), educational level (6 categories; from ≤9 years to postgraduate), exercise habits (5 levels; from never to ≥6 times/week), smoking (5 levels; from never to ≥20 cigarettes/day), BMI (4 levels; from underweight to obese), somatic and psychiatric co-morbidity (yes/no for each disorders) (Model 3), overall perceived health (5 levels; from very bad to very good), and use of mood stabilizing medication (yes/no), insomnia (very often or often/no), and perceived loneliness (very often or often/no) (Model 4). To study any moderating effects of sex, age, educational level, and occupational group, an interaction term was introduced in model 3 (which included the full sample) in the Cox regression analysis for each outcome. Interactions were defined as $p <$ 0·05 for the interaction term. In separate stratified analyses, the moderators were dichotomized as men/women, younger (≤54 years)/older (>54 years), short (<12 years)/middle or long (≥12 years) educational attainment, and white/blue collar occupational groups. The cut-off for

age dichotomization was chosen as the mean age of menopause for women in Sweden (Dratva et al., 2009).

A sensitivity analysis was performed to address reverse causality. We excluded cases who had received the outcome within 2 years after the HPA and compared the results to the full cohort.

Statistical analyses were performed by using SPSS (SPSS, 2024) and R (version 4.2.1) with Tidyverse, Survival, Splines, and Patchwork package (R Core Team, 2021).

3. Results

330,247 participants without a diagnosis of depression at baseline were included (mean age 42·4 (SD 11·1) years, 46·2% women). Of the included participants, 2619 (0·9%) individuals received a diagnosis of depression during mean follow-up of 10·0 (SD 5·5) years, 12,429 (3·8%) individuals had at least one period of long-term sickness absence due to depression (mean follow up 10·3 (SD 5·6) years), and 512 (0·2%) individuals received disability pension due to depression (mean follow up 11·0 (SD 5·5) years). Mean estimated VO_2max was 36·4 (SD 10·0) ml/min/kg at baseline, and BMI 25·6 kg/m^2 (SD 4·1) (Table 1). Eighty-eight percent had no co-morbidities, with only 1·3% having two or more co-morbidities.

CRF associated beneficially from low (≈22 ml/min/kg) to higher levels with incident depression and long-term sickness absence risk, and from moderate levels (≈35 ml/min/kg) with disability pension risk (Fig. 1). After additional adjustments for lifestyle-related factors (educational level, exercise habits, smoking, BMI) and somatic and psychiatric co-morbidities, participants with moderate (32–46 ml/min/kg) and high (≥46 ml/min/kg) CRF still had a significantly lower risk for incident depression compared to very low CRF (<25 ml/min/kg), HR (95% CI): 0·84 (0·73–0·97) and 0·80 (0·66–0·96) (Table 2). Associations with long-term sickness absence as well as disability pension due to depression weakened after adjustment for lifestyle-related factors and co-morbidity so that only participants with high CRF had a significantly lower risk compared to low CRF, HR = 0·84 (0·77–0·91) for long-term sickness absence. For disability pension the association became non-significant HR = 0·70 (0·46–1·08). All statistically significant associations above remained stable in the sub-sample with additional adjustment for overall perceived health, and use of mood stabilizing medication at baseline, insomnia, and perceived loneliness (model 4). Further, the sensitivity analysis to address reverse causality showed similar effect sizes for high CRF for incident depression and long-term sickness absence, but results were non-significant. The effect sizes were weakened for all CRF groups for risk of disability pension due to depression. Exclusion of participants self-reporting frequent use of mood stabilizing medication at baseline did not alter the results.

3.1. Moderation analyses

Sex moderated the association between CRF and incident depression ($p = 0·014$) as well as long-term sickness absence due to depression ($p < 0·001$), indicating that the overall beneficial association with higher CRF was only present in men (Table 3 and Appendix Fig. C.1–9.). Further, age moderated the association between CRF and long-term sickness absence ($p < 0·001$) and disability pension ($p < 0·001$), with generally more beneficial associations seen with higher CRF in participants <54 years at baseline. Level of education moderated the association between CRF and incident depression ($p = 0·008$) and long-term sickness absence ($p < 0·001$). Participants with short education had a more beneficial association with higher CRF. Occupational group did not moderate any of the associations.

4. Discussion

Main findings in this study using a large sample of Swedish workers were that higher CRF was strongly associated with subsequent lower

Table 1
Descriptive statistics on adult study participants followed over time with data from Swedish occupational health screenings, stratified on levels of CRF (n = 330,247), collected between October 1982 until December 2020.

	Total sample n (%)	Very low CRF (<25 ml/min/kg) n (%)	Low CRF (25 to < 32 ml/min/kg) n (%)	Moderate CRF (32 to < 46 ml/min/kg) n (%)	High CRF (≥46 ml/min/kg) n (%)
	330,247 (100)	38,214 (11·6)	82,005 (24·8)	154,886 (46·9)	55,142 (16·7)
Mean CRF (ml/min/kg)	36·4 (10·0 SD)	–	–	–	–
Mean age (years)	42·4 (11·1 SD)	49·9 (9·7 SD)	46·4 (10·3 SD)	41·1 (10·7 SD)	36·2 (9·2 SD)
≤50 years	241,114 (73.0)	17,700 (46·3)	50,081 (61·1)	121,789 (78·6)	51,544 (93·5)
Sex (women)	152,459 (46.2)	19,271 (50·4)	38,571 (47·0)	70,159 (45·3)	24,458 (44·4)
BMI (kg/m^2)	25·6 (4·1 SD)	29·8 (5·2 SD)	26·9 (4·0 SD)	24·9 (3·3 SD)	23·1 (2·5 SD)
Daily smoking (≥1 cigarette/day)	32,362 (9·8)	5251 (13·7)	9930 (12·1)	13,956 (9·0)	3225 (5·8)
Educational level (≥12 years)	300,446 (91·0)	32,167 (84·2)	72,343 (88·2)	143,120 (92·4)	52,816 (95·8)
Exercise habits (≥1 time/week)	219,575 (66·5)	19,037 (49·8)	46,924 (57·2)	107,473 (69·4)	46,141 (83·7)
Co-morbidity					
Other psychiatric	1996 (0·6)	232 (0·6)	533 (0·6)	927 (0·6)	304 (0·6)
Cardiovascular disease	14,875 (4·5)	2991 (7·8)	4971 (6·1)	5822 (3·8)	1091 (2·0)
Cancer	11,251 (3·4)	2060 (5·4)	3633 (4·4)	4693 (3·0)	865 (1·6)
Musculoskeletal	15,174 (4·6)	2555 (6·7)	4499 (5·5)	6511 (4·2)	1609 (2·9)
Number of co-morbidities					
0	291,420 (88·4)	31,383 (82·1)	69,915 (85·3)	138,610 (89·5)	51,512 (93·4)
1	34,625 (10·5)	5880 (15·4)	10,646 (12·9)	14,702 (9·5)	3397 (6·2)
≥2	4202 (1·3)	951 (2·5)	1444 (1·8)	1574 (1·0)	233 (0·4)
Perceived health (very poor/poor)	18,036 (5·5)	3811 (10·0)	5575 (6·8)	7180 (4·6)	1470 (2·7)
Use of mood stabilizing medication at baseline (very often/often)	9656 (2·9)	1558 (4·1)	2801 (3·4)	4121 (2·7)	1176 (2·1)
Insomnia (very often/often)	62,210 (21·4)	8585 (25·9)	16,853 (23·4)	28,245 (20·6)	8528 (17·4)
Perceived loneliness (very often/often)	7293 (2·6)	931 (2·9)	1809 (2·6)	3326 (2·5)	1227 (2·6)
Occupational group					
White-collar	246,389 (74·6)	27,160 (71·1)	59,115 (72·1)	116,413 (75·2)	43,701 (79·3)
Blue collar	83,858 (25·4)	11,054 (28·9)	22,890 (27·9)	38,473 (24·8)	11,441 (20·7)
Incident depression	2619 (0·9)	362 (0·9)	717 (0·9)	1162 (0·8)	378 (0·7)
Follow-up time, years	10.0 (5·5 SD)	9·4 (5·4 SD)	9·9 (5·5 SD)	10·2 (5·5 SD)	10·2 (5·6 SD)
Sick leave due to depression	12,429 (3·8)	1420 (3·7)	3154 (3·8)	5968 (3·9)	1887 (3·4)
Follow-up time, years	10·3 (5·6 SD)	9·7 (5·4 SD)	10·2 (5·5 SD)	10·4 (5·5 SD)	10·5 (5·6 SD)
Disability pension due to depression	512 (0·2)	86 (0·2)	157 (0·2)	227 (0·1)	42 (0·1)
Follow-up time, years	11·0 (5·5 SD)	10·4 (5·4 SD)	10·8 (5·5 SD)	11·1 (5·5 SD)	11·1 (5·6 SD)

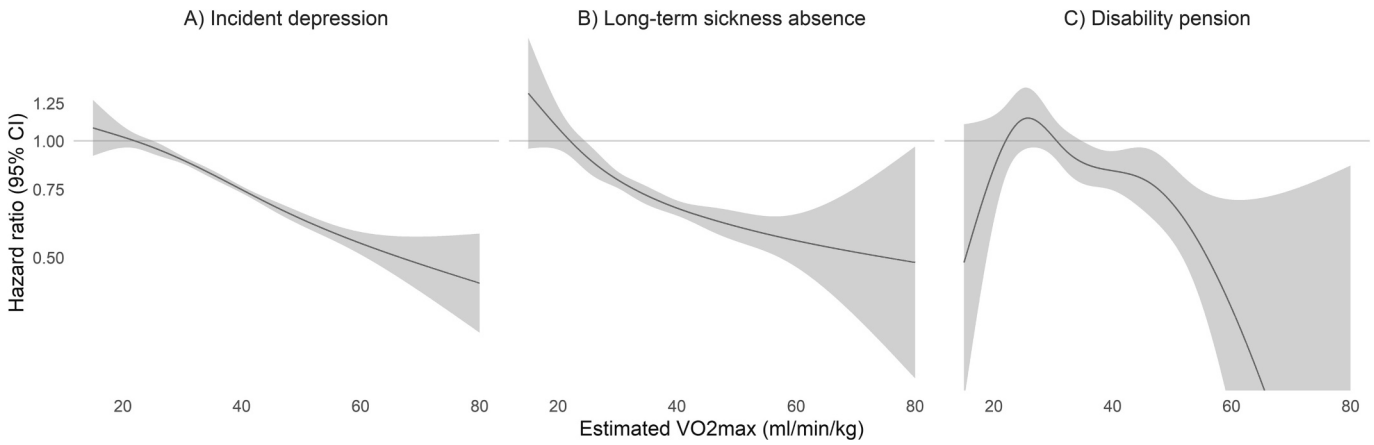

Fig. 1. Association between continuous levels of estimated VO_2max and incident depression, long-term sickness absence, and disability pension due to depression in Swedish occupational health screenings, 1982–2020.
Adjusted for sex and age. Reference set to 22 ml/min/kg, and knots to 25, 32, 46 ml/min/kg.

Table 2
Associations (hazard ratio and 95% confidence intervals) between incident depression, long-term sickness absence due to depression, and receiving disability pension due to depression in relation to estimated VO_2max in Swedish occupational health screenings, 1982–2020.

	Model 1	Model 2	Model 3	Model 4	Model 3 – exclusion cases two first years
	Incident depression				
Cases (n)/Total (N)	2619/330,247	2619/330,247	2619/330,247	2490/281,294	1943/302,258
Per ml/min/kg of estimated VO_2max	0·99 (0·98;0·99)	0·98 (0·98;0·99)	0·99 (0·99;1·00)	0·99 (0·99;1·00)	0·99 (0·99;1·00)
Very low (<25 ml/min/kg)	1·00 (ref)	1·00 (ref)	1·00 (ref)	1·00 (ref)	1·00 (ref)
Low (25 to <32 ml/min/kg)	0·90 (0·78;1·03)	0·88 (0·77;1·01)	0·96 (0·83;1·10)	0·94 (0·82;1·09)	0·99 (0·84;1·15)
Moderate (32 to <46 ml/min/kg)	0·75 (0·66;0·85)	0·70 (0·61;0·80)	0·84 (0·73;0·97)	0·84 (0·72;0·97)	0·88 (0·75;1·04)
High (≥46 ml/min/kg)	0·70 (0·60;0·81)	0·61 (0·52;0·72)	0·80 (0·66;0·96)	0·79 (0·65;0·96)	0·81 (0·66;1·00)
	Long-term sickness absence				
Cases (n)/Total (N)	12,429/330,247	12,429/330,247	12,429/330,247	11,707/281,294	8960/298,585
Per ml/min/kg of estimated VO_2max	1·00 (0·99;1·00)	0·98 (0·98;0·99)	0·99 (0·99;1·00)	1·00 (0·99;1·00)	1·00 (0·99;1·00)
Very low (<25 ml/min/kg)	1·00 (ref)	1·00 (ref)	1·00 (ref)	1·00 (ref)	1·00 (ref)
Low (25 to <32 ml/min/kg)	1·00 (0·94;1·07)	0·92 (0·87;0·98)	1·03 (0·97;1·10)	1·06 (0·99;1·13)	1·06 (0·98;1·15)
Moderate (32 to <46 ml/min/kg)	0·99 (0·93;1·04)	0·79 (0·74;0·83)	0·99 (0·93;1·06)	1·04 (0·97;1·11)	1·06 (0·98;1·15)
High (≥46 ml/min/kg)	0·87 (0·81;0·93)	0·59 (0·55;0·64)	0·84 (0·77;0·91)	0·89 (0·82;0·97)	0·92 (0·83;1·02)
	Disability pension				
Cases (n)/Total (N)	512/330,247	512/330,247	512/330,247	473/281,294	353/315,314
Per ml/min/kg of estimated VO_2max	0·97 (0·96;0·98)	0·99 (0·97;0·99)	0·99 (0·98;1·00)	0·99 (0·98;1·00)	1·00 (0·98;1·01)
Very low (<25 ml/min/kg)	1·00 (ref)	1·00 (ref)	1·00 (ref)	1·00 (ref)	1·00 (ref)
Low (25 to <32 ml/min/kg)	0·83 (0·64;1·08)	0·95 (0·73;1·24)	1·03 (0·78;1·35)	0·99 (0·75;1·30)	0·90 (0·64;1·27)
Moderate (32 to <46 ml/min/kg)	0·63 (0·49;0·80)	0·85 (0·66;1·10)	1·02 (0·77;1·35)	0·99 (0·74;1·32)	1·02 (0·72;1·45)
High (≥46 ml/min/kg)	0·32 (0·22;0·47)	0·54 (0·36;0·79)	0·70 (0·46;1·08)	0·68 (0·43;1·06)	0·76 (0·46;1·27)

Model 1; Crude.
Model 2; Model 1+ sex and age.
Model 3; Model 2 + educational level, exercise habits, smoking, BMI, and somatic and psychiatric co-morbidity.
Model 4; Model 3 + overall perceived health, and use of mood stabilizing medication at baseline, insomnia, and perceived loneliness.

incident depression risk, as well as lower risk of long-term sickness absence due to depression during a mean time of 10·0 years follow-up. These associations remained stable after adjusting for lifestyle-related factors and co-morbidities. The associations were attenuated in sensitivity analyses excluding cases within two years after baseline examination, indicating the possibility, at least partly, of bidirectional associations. Hence, it is difficult to disentangle whether the low CRF and thereby low exercise intensity, is causing the depression or if individuals who are depressed might feel less motivated to exercise at a high intensity level. Moreover, sex, age, and educational level moderated the associations between CRF and the outcomes, indicating that overall beneficial associations with higher CRF were mainly evident in men, younger participants, and lower education.

The present study is novel in investigating not only the association of CRF and incident depression but also further effects of depression such as long-term sickness absence and disability pension due to depression. We confirm findings from previous studies investigating one or more of these outcomes. Low and medium CRF has been associated with an overall higher risk of depression (Kandola et al., 2019; Schuch et al., 2016b) and depression symptom severity in both healthy and depressed adults (Papasavvas et al., 2016), and CRF has been inversely associated in cross-sectional analyses with short-term sickness absence among military personnel (Kyrolainen et al., 2008), office workers (Drake et al., 2020), and municipal workers (Kolu et al., 2022). In one million young men, low CRF at conscript was associated with a four-fold increased risk of receiving disability pension due to psychiatric diagnoses later in life (mean follow-up 28 years) (Henriksson et al., 2019). The study only included men and no analyses of CRF in adulthood closer to the event. Our study extends previous findings by including both men and women, evaluating mid-life CRF, and adjusting for multiple covariates and co-morbidities.

Mechanisms associating CRF with incident depression are not fully understood. Level of CRF may be viewed as an objective measure of, and to strongly depend on, recent levels of exercise, which in turn has been associated with antidepressant effects in both individuals with and without clinical depression (Bellon et al., 2021; Schuch et al., 2016a).

Table 3
Associations (hazard ratio and 95% confidence intervals) between incident depression, long-term sickness absence due to depression, and receiving disability pension due to depression in relation to estimated VO_2max in Swedish occupational health screenings, 1982–2020. Analyses are stratified on sex, age, educational level, and occupation for each outcome.

		Estimated VO_2max (ml/min/kg)			
	Interaction analyses	Very low (<25)	Low (25 to <32)	Moderate (32- <46)	High (≥ 46)
	Incident depression				
Women [a] (*n* = 1323)	Sex*CRF, p = 0·014	1·00 (ref)	1·13 (0·93; 1·36)	0·95 (0·78; 1·16)	0·98 (0·76; 1·26)
Men [a] (*n* = 1026)		1·00 (ref)	0·76 (0·62; 0·94)	0·69 (0·56; 0·86)	0·59 (0·45; 0·79)
≤54 years [b] (*n* = 1025)	Age*CRF, p = 0·078	1·00 (ref)	0·90 (0·74; 1·08)	0·73 (0·60; 0·89)	0·68 (0·51; 0·91)
>54 years [b] (*n* = 1324)		1·00 (ref)	1·02 (0·82; 1·26)	0·95 (0·76; 1·18)	0·92 (0·71; 1·20)
Short education <12 years [c] (*n* = 351)	Education*CRF, p = 0·008	1·00 (ref)	0·90 (0·74; 1·08)	0·73 (0·60; 0·89)	0·68 (0·51; 0·91)
Middle/long ≥12 years [c] (*n* = 2268)		1·00 (ref)	1·02 (0·82; 1·26)	0·95 (0·76; 1·18)	0·92 (0·71; 1·20)
White-collar [b] (*n* = 1700)	Occupational group*CRF, p = 0·314	1·00 (ref)	0·97 (0·82; 1·15)	0·83 (0·70; 0·98)	0·81 (0·65; 1·01)
Blue-collar [b] (*n* = 649)		1·00 (ref)	0·93 (0·71; 1·20)	0·87 (0·66; 1·14)	0·76 (0·53; 1·10)
	Long-term sickness absence				
Women [a] (*n* = 7995)	Sex*CRF, *p* < 0·001	1·00 (ref)	1·12 (1·04; 1·22)	1·17 (1·07; 1·27)	1·06 (0·95; 1·18)
Men [a] (*n* = 3996)		1·00 (ref)	0·92 (0·82; 1·04)	0·81 (0·72; 0·91)	0·62 (0·53; 0·72)
≤54 years [b] (*n* = 11,037)	Age*CRF, p < 0·001	1·00 (ref)	1·00 (0·93; 1·08)	0·97 (0·90; 1·05)	0·85 (0·77; 0·93)
>54 years [b] (*n* = 954)		1·00 (ref)	1·02 (0·86; 1·21)	0·96 (0·80; 1·16)	1·00 (0·66; 1·52)
Short education <12 years [c] (*n* = 4397)	Education*CRF, p < 0·001	1·00 (ref)	1·03 (0·94; 1·14)	0·98 (0·89; 1·09)	0·85 (0·73; 0·98)
Middle/long ≥12 years [c] (*n* = 7594)		1·00 (ref)	1·03 (0·94; 1·13)	1·02 (0·93; 1·12)	0·89 (0·80; 1·00)
White-collar [b] (*n* = 9416)	Occupational group*CRF, p = 0·211	1·00 (ref)	1·07 (0·99; 1·15)	1·06 (0·98; 1·15)	0·91 (0·83; 1·01)
Blue-collar [b] (*n* = 2575)		1·00 (ref)	1·03 (0·90; 1·18)	0·98 (0·85; 1·13)	0·82 (0·68; 0·99)
	Disability pension				
Females [a] (*n* = 362)	Sex*CRF, p = 0·085	1·00 (ref)	1·05 (0·75; 1·47)	1·06 (0·75; 1·50)	0·71 (0·42; 1·18)
Males [a] (*n* = 114)		1·00 (ref)	0·73 (0·43; 1·24)	0·60 (0·34; 1·06)	0·51 (0·21; 1·24)
≤54 years [b] (*n* = 370)	Age*CRF, p < 0·001	1·00 (ref)	0·74 (0·53; 1·04)	0·77 (0·55; 1·09)	0·61 (0·38; 0·99)
>54 years [b] (*n* = 106)		1·00 (ref)	1·26 (0·76; 2·09)	0·95 (0·54; 1·68)	0·32 (0·04; 2·44)
Short education <12 years [c] (*n* = 234)	Education*CRF, p = 0·109	1·00 (ref)	0·79 (0·55; 1·14)	0·68 (0·46; 1·01)	0·50 (0·26; 0·98)
Middle/long education ≥12 years [c] (*n* = 242)		1·00 (ref)	1·16 (0·74; 1·82)	1·19 (0·75; 1·89)	0·86 (0·46; 1·61)
White-collar [b] (*n* = 387)	Occupational group*CRF, p = 0·749	1·00 (ref)	1·03 (0·75; 1·41)	0·96 (0·69; 1·35)	0·68 (0·42; 1·12)
Blue-collar [b] (*n* = 89)		1·00 (ref)	0·72 (0·39; 1·33)	0·76 (0·40; 1·45)	0·51 (0·18; 1·48)

[a] Adjusted for age, education level, exercise habits, smoking, BMI, and somatic and psychiatric co-morbidity.
[b] Adjusted for sex, age, education level, exercise habits, smoking, BMI, and somatic and psychiatric co-morbidity.
[c] Adjusted for sex, age, exercise habits, smoking, BMI, and somatic and psychiatric co-morbidity.

Exercise has been suggested to influence the structural functioning of the brain (such as the hippocampus) (Gujral et al., 2017), as well as symptoms (e.g., cognitive, emotional, and somatic) and molecular (e.g., HPA axis homeostasis, anti-neurodegenerative and neuroimmune functioning), changes related to depressive disorders (Archer et al., 2014). Moreover, exercise and higher CRF may reduce systemic inflammation and improve endothelial dysfunction, which are implicated in the pathogenesis of atherosclerosis and neurodegeneration and the subsequent development of common health disorders including depression (Pedersen, 2009). Depending on the mechanism employed to explain the relationship between CRF and depression, exercise may be viewed either as a mediator or a confounder in the relationship. However, evidence also implicates that the beneficial role of CRF may be explained regardless of exercise. For example, CRF, and not physical activity, is suggested to have a positive relationship with functional connectivity of several cortical networks of the brain relevant to age-related changes in cognition and risk of neurological diseases (Voss et al., 2016). A recent trial showed that improvements in VO_2max, regardless of exercise intensity or frequency, predicted a more significant reduction in depression severity among clinically depressed (Rahman et al., 2018). Shared genetics is another possible pathway, where genetic links between CRF and CVD risk (Bye et al., 2020), as well as regular exercise and risk for Alzheimer's disease (Klimentidis et al., 2018), have been reported.

Regarding sickness absence and disability pension, mechanisms are multifaceted and may be even more complex than for incident depression. Some may be directly associated with the work situation (such as the ability/capacity to adapt to work tasks). Others have been linked to structural and economic factors. For example, individuals in occupations in Sweden with lower income and educational requirements are shown to be more prone to long-term sickness absence (Skandia, 2021. https://www.skandia.se/globalassets/pdf/press-och-media/rapporter-och-debatt/sveriges-sjukaste-yrke-2021-.pdf [Accessed 2022-12-22]). If there are separate causal relationships between CRF and depression, these pathways must be addressed separately and explored in further studies.

This is, to the best of our knowledge, the first large-scale study showing moderating effects by sex, age, and educational level on the associations between CRF and incident depression, long-term sickness absence, and disability pension. Although depression incidence and

related outcomes were more prevalent in women in the present study, the beneficial association of higher CRF was only evident in men. This is in line with one previous study including both healthy and depressed adults, where correlations between depression symptom severity and CRF were evident in both men and women, however stronger in men (Papasavvas et al., 2016). This is contradictory to a more protective role for physical activity on depression onset mainly seen in women (Mammen and Faulkner, 2013). While psychological aspects, such as stronger social benefits of physical activity engagement, have been postulated to explain the latter associations, the stronger associations of CRF in men can only be speculated on. Sex differences in brain function in major depressive disorder patients (Tu et al., 2022), as well as in neurotransmitter system and hormonal factors (Accortt et al., 2008), are some possible explanations. Similar speculations may be made for the variation between younger and older participants. For the stronger associations in those with short education, one possibility may be that CRF has a predictive value beyond that of the physiological status of the cardiorespiratory system, but also that CRF captures the complex variation in other attributes central for depression risk and related outcome. This may include obesity, smoking, social and socioeconomic factors, which have previously been linked to both exercise levels and CRF, and level of education (Puka et al., 2022).

The present results are of high clinical, societal, and public health policy relevance, as the burden of depression is already high (Collaborators, 2021). For example, according to prognostic calculations, it is expected that 43% of new non-communicable disease cases worldwide will result from depression, accounting for 28% of total direct healthcare costs(World Health Organization, 2022). This only includes costs for the depression case per se and not the additional cost for a possible simultaneous increase in sickness absence and disability pension due to the increase in depression cases. In addition, we recently published data on historical trends in CRF based on the present database used, including over 350,000 men and women, showing a decline in CRF over the last two decades (Ekblom-Bak et al., 2019). The decline was more pronounced in men, younger ages, and low educational individuals. In forecasts we calculated, prognostic analyses indicated a continued downward trend of cardiovascular fitness, especially in participants with low educational level (Vaisanen et al., 2021).

4.1. Study limitations and strengths

A strength of the present study was the large sample of men and women without previous diagnosis of depression at baseline. CRF was objectively assessed through exercise testing. The use of national registers to identify both incident cases of depression, long-term sickness absence, and disability pension enabled investigation on the impact of CRF on both individual and societal effects of depression incidence (incident depression, more individual burden; long-term sickness absence and disability pension, additional large burden for society). Using the national patient registry ensures an objectively evaluated depression diagnosis, however it also most likely captures more severe cases of depression as milder cases would seek healthcare in the primary care system. This limits the generalizability of our results to the full spectrum of depression severity. This limitation is partly compensated for by also analyzing the association between CRF and long-term sickness absence as these individuals largely have received their primary care diagnosis. Additional strengths were the evaluation of potential moderators and the inclusion of relevant lifestyle factors, co-morbidity, and other mood-related variables in the analyses. Limitations include that the sample was relatively young and somewhat biased by selection, and the generalizability of the results to a population with other characteristics should been done with caution. Also, the attenuated association in sensitivity analyses after exclusion of cases within two years of baseline examination indicates bidirectional associations, which should be considered when interpreting the results. Although the menopause phase may be relevant, we could not take individual variations of it into account. Finally, although the question of genetic contribution on both CRF level and physical activity behavior are important factors to evaluate we could not account for this in the study. Future research should aim to factor in genetic liability, especially when designing intervention studied aiming to change behavior.

5. Conclusion

The findings of this present study show that CRF can be used as a marker for future depression and related consequences, as moderate to high levels of CRF were related to a lower risk of future incident depression, and some extent long-term sickness absence due to depression. This seems particularly important in men, younger individuals, and in those with short education. If the found relationships are causal, targeted interventions focusing on increasing CRF in these sub-groups should be prioritized. More research on the duration, frequency, intensity, and mode of exercise to maximize the beneficial effects of CRF on depression outcomes in different groups should be conducted.

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Data sharing statement

The data underlying the findings in our study are not publicly available because the original approval by the regional ethics board and the informed consent from the subjects participating in the studies did not include such a direct, free access. Data are owned by and can be requested from the HPI Health Profile Institute at support@hpihealth.se.

CRediT authorship contribution statement

Camilla A. Wiklund: Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Örjan Ekblom:** Writing – review & editing, Conceptualization. **Sofia Paulsson:** Resources, Data curation. **Magnus Lindwall:** Writing – review & editing, Conceptualization. **Elin Ekblom-Bak:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sofia Paulsson is employed by the HPI Health Profile Institute, which has provided the data used in the study. There is no other competing interest.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2024.107916.

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