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RESEARCH ARTICLE

Change in Cardiorespiratory Fitness and Risk of Depression, Anxiety, and Cerebrovascular Disease

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Introduction: High cardiorespiratory fitness (CRF) has been associated with a lower risk of depression, anxiety, and cerebrovascular disease. The aim was to explore CRF changes over-time associated with these outcomes.

Methods: This large-scale prospective cohort study, using data from Swedish population-wide registries and databases (during 1972−2020), included men (n=131,431), with measures of estimated CRF (estCRF) in late adolescence (maximal cycle test) and adulthood (submaximal cycle test) (mean years between 24.6, SD 8.8). The study explored how change in estCRF was associated with incident depression, anxiety, and cerebrovascular disease using Cox proportional hazards models. Analyses were performed in 2023.

Results: Higher estCRF in late adolescence and adulthood were associated with a lower risk of incident depression, anxiety, and cerebrovascular disease later in life. For all three outcomes, an increase in estCRF (mL/min/kg and z-score) between the two-time points was associated with a lower risk. Further, decreasing from moderate or high estCRF in adolescence to low estCRF in adulthood, compared to staying at a moderate or high level, was associated with a higher risk of depression and anxiety (HR: 1.24 95% CI 1.07−1.45 and 1.25 95% CI 1.06−1.49, respectively). Conversely, increasing from moderate to high estCRF was associated with a lower risk of incident anxiety (HR: 0.84 95% CI 0.71−0.99).

Conclusions: The findings indicate that there is a longitudinal association between negative change in estCRF and increased risk of depression, anxiety, and cerebrovascular disease later in life. Decreasing levels of estCRF could be a helpful indicator when identifying these disorders at a population level.

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INTRODUCTION

A well-established positive relationship exists between regular physical activity and several aspects of health, including brain health.[1] Depression and anxiety are highly prevalent and leading causes of disability in the world.[2,3] Apart from having an impact on both individual and societal levels, depression and anxiety are also linked to increased risk for stroke and dementia through both structural, hemodynamic, and inflammatory pathways.[4,5] Common for these conditions is the possible importance of modifiable lifestyle factors for both prevention and treatment, as they may be directly amenable to interventions. High

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cardiorespiratory fitness (CRF) is a modifiable lifestyle factor that depends on the current moderate-to-vigorous physical activity[6] but is also substantially influenced by a genetic contribution.[7] CRF has previously been linked to anxiety and depression[8−13] as well as cerebrovascular diseases (defined as medical conditions affecting the blood vessels of the brain), for example, stroke[14] and vascular dementia,[15−19] in both clinical and healthy population samples. Studies indicate that individuals with low CRF are at higher risk of these adverse outcomes than those with high or moderate CRF. Rahman et al.[20] suggested that improvements in CRF predict a greater reduction in depression severity among individuals who were clinically depressed. Moreover, Henriksson et al.[21] found that low CRF in late adolescence was strongly associated with chronic disability due to psychiatric causes later in life.

Few studies are available investigating changes in CRF during adulthood and the risk of anxiety and depression. Including small samples and/or nonexercise tests, studies have found consistent or increasing CRF to be beneficial.[22−24] Both baseline and increase in CRF over 7 years were associated with changes in long-term risk of stroke and death.[17] An improved or maintained CRF in adulthood was associated with a lower risk for hypertension and better self-rated health, compared to lowered CRF.[25,26] Tari et al.[27] showed that change in estimated (nonexercise tested) CRF over 10 years was an independent risk factor for dementia (including vascular dementia) incidence and mortality.

As both exercise and CRF can be expected to vary over the life course, examining their associations with anxiety, depression, and cerebrovascular disease throughout life can provide insight into the dynamics of these associations. This study aimed to explore how change between CRF in late adolescence and adulthood is associated with incident anxiety, depression, and cerebrovascular disease later in life in a large sample of Swedish men. Maintenance of low CRF or decrease in CRF between late adolescence and adulthood was hypothesized to be associated with higher risk for incident anxiety and depression, and cerebrovascular disease. Further, a curvilinear relationship was hypothesized, meaning that males who decrease their CRF will have a higher risk than those who maintained a moderate or high CRF or increased their CRF.

METHODS

Study Population

In this large-scale prospective observational study, exposure data from the Swedish military service conscription register (late adolescence) and Swedish occupational health screenings (adulthood) were combined with outcome data from Swedish national registers to follow males over time. Using the Swedish unique personal identification number,[28] men who had undergone conscription between 1972 and 2005 (mean age 18.3, SD 0.7) and a Health Profile Assessment (HPA) through occupational health services in adulthood (between 1986 and 2020, mean age 43.3, SD 11.2) were identified. During the included years, military conscription was compulsory for all males in Sweden and the coverage for the included birth cohorts ranges from 82% to 94%.[28] Data from 136,771 men with valid estimated CRF (estCRF) data on both occasions were included. Of these, 4,340 were lacking data on covariates. Hence, 131,431 men with valid data from both conscription and HPA and linked with outcome data from national registers, were included (Appendix Figure 1). Diagnoses of depression, anxiety, stroke, and/or vascular dementia before the CRF test in adulthood were excluded. Informed consent to participate in the HPA database was given at the HPA. The study was approved by the Stockholm Ethics Review Board (Dnr:462-14,579-15; 2020−03667/462−14) and adhered to the Declaration of Helsinki.

Participants were identified in the Swedish military service conscription register,[29] with valid data on estCRF, date of performed conscription, and being male as inclusion criteria. EstCRF was assessed using a maximal work tolerance test on a cycle ergometer, expressed as total maximal work tolerance in Watts (Wattmax). Before 1980, Wattmax was defined as the maximal work rate an individual could sustain for 6 minutes from an incremental all-out test, with 50-watt increments each fourth minute. After 1980, Wattmax was calculated based on the highest achieved work rate from an incremental test with 25-watt increases each minute. Both maximal tests were carried out at a cadence of 60 or 60-70 rpm. The tests and their differences have previously been described in detail.[29] For comparative reasons, Wattmax was translated into absolute maximal oxygen uptake, VO_2max (L/Min), using the formula: $VO_2max=0.01031\times Wattmax+0.72$ (until 1980) and the formula $VO_2max=(0.938\times Wattmax-38.2)\times 0.01031+0.72$ (1980 and onwards). The following information from the conscription was included: year, age, site, IQ, and BMI. IQ was assessed with a standardized test battery and calculated into a stanine score (1−9). BMI was calculated as weight in kilograms divided by height in meters squared. For further details on the testing procedures, see Ludvigsson et al.[29]

The HPA database includes data from HPAs performed in occupational health services since the early 1990s. Participation in an HPA is optional and free of charge for the individual and offered to employees

working for a company or organization connected to occupational or other health services. An HPA comprises of a lifestyle and perceived health questionnaire, a physical examination, and an in-depth interview with a HPA coach. The HPI Health Profile Institute (Stockholm, Sweden) is responsible for educating HPA coaches, managing the database, and developing software for data collection. At the HPA, CRF was estimated using the Åstrand submaximal test on an ergometer cycle. The individual cycles for 6 minutes on a constant workload, and the steady-state heart rate response during the last minute is used to estimate VO_2max (in L/Min).[30,31] The submaximal protocol has been reported to produce valid and reliable estimations comparable to directly measured V̇O2max.[32] Further, body weight was assessed to the nearest 0.5 kg. Body height was measured to the nearest 0.5 cm. BMI was subsequently calculated. Additional lifestyle factors were self-reported (Appendix Table 1).

Measures

The primary exposure was change in estCRF between late adolescence and adulthood. Due to the different modes and nature of the tests used at conscription and HPA, change in estCRF was assessed in two different ways, both as (1) change in z-score and (2) change in absolute estCRF, expressed as L/min and mL/min/kg. More specifically, for (1) late adolescent estCRF, a standardized score (z-score) was calculated using the individual Wattmax minus the mean Wattmax for each year, divided by the SD of Wattmax for each year. For adulthood assessment, a z-score was calculated using the same formula but using mL/min/kg within a 5-year age interval for the test, to account for the large age range in adult measurements performed. Change in estCRF was subsequently calculated as the delta value between late adolescent and adulthood z-score. For (2) change was assessed as change in VO_2max from late adolescence to adulthood estCRF. To account for the significant individual variation in time between the two CRF assessments, the annual percent change in estCRF in both L/min and mL/min/kg was calculated.

Primary outcomes included incident anxiety, depression, and stroke/vascular dementia. Participants were followed from HPA in adulthood until the incidence of the specific outcome, death, or 31 of December 2019, using linkage to the Swedish national patient registry, the national out-patient registry, and the cause of death registry. Stroke and vascular dementia were combined into one variable (cerebrovascular disease) due to the small number of cases receiving these diagnoses. To retrieve the diagnosis of each disorder/disease, ICD-10 codes (or equivalent codes from ICD-9/8) were used (depression: F32−34, F38; anxiety: F41; cerebrovascular disease: I60−I64, G45, F01).

Analyses were adjusted for several potential confounders/covariates that could influence the relationship between the exposure and the outcomes. In late adolescence, the following covariates were considered: year, age, site of conscription, IQ, and BMI. In adulthood, the following covariates were considered: age, BMI, exercise habits, smoking, perceived loneliness, perceived general health, and self-reported stress. In addition, the analyses were adjusted for common co-morbidity defined as lifetime presence of any of the following categories: Cardiovascular disease (ICD-10; I00−I99, except I60−I64), cancer (ICD-10; C00-D48), and other psychiatric disorders (ICD-10; F00, F02−F09, F20−F29, F30−31). Each category was coded into yes or no (1/0) and was then summed into a 0−3 range of co-morbidity.

Statistical Analysis

The association between late adolescent estCRF (in L/min) and the three outcomes was analyzed in three separate models using Cox-regression analyses (obtaining HRs with 95% CIs) while controlling for estCRF at the adult assessment. The same analysis was repeated for adult estCRF (in L/min) and the three outcomes. Change was analyzed as a continuous variable (as change in z-score and annual percent change in VO_2max) and as a categorical variable. The categories were defined as 1 SD above (high) and below (low) the mean (moderate) z-score at each time point. Change was then defined as change in CRF category between the two-time points. Crude analysis of the total population for all models was performed and then the adjustments for confounders and covariates were added. To visualize the results, restricted cubic splines with knots at the 5th, 50th, and 95th percentile for all VO_2max outcomes, with the 50th percentile as the reference was performed. Sensitivity analyses were performed excluding cases during the first 2 years after HPA to study possible reversed causality. Statistical analyses were performed in 2023 using R, version 4.2.1.[33]

RESULTS

The study included 131,431 male participants with CRF assessments in late adolescence and adulthood. Mean estimated VO_2max was 47.4 (6.7) mL/min/kg in late adolescence and 36.5 (SD 9.8) mL/min/kg at adulthood (Table 1). During a mean follow-up time of 8.3 (SD 5.4) years after adulthood assessment, there were a total of 1,915 (1.5%) incident cases of depression, 1,626 (1.3%) incident cases of anxiety, and 799 (0.6%) incident cases of cerebrovascular disease.

Table 1. Descriptive Data of the Included Participants

Population characteristics	Late adolescence	Adulthood
Age, years (mean (SD))	18.3 (0.7)	42.9 (8.9)
Estimated VO_2max, mL/min/kg (mean (SD))	47.5 (6.7)	36.6 (9.9)
Estimated VO_2max, L/min (mean (SD))	3.3 (0.4)	3.1 (0.8)
BMI, kg/m^2 (mean (SD))	21.8 (2.7)	26.5 (3.8)
IQ, scale 1−9, (mean (SD))	5.4 (1.9)	-
Daily smoking (≥1 cigarette/day, *n* (%))	-	7,094 (6.9%)
Exercise habits (≥1 time/week, *n* (%))	-	76,742 (58.4%)
Co-morbidity in adulthood (*n*, %)		
No co-morbidities	-	55,340 (42.7%)
≥ 2 co-morbidities	-	31,951 (24.3%)
Perceived stress (very often/often, *n* (%))	-	10,871 (10.6%)
Perceived overall health (very poor/poor, *n* (%))	-	5,157 (5.0%)
Perceived loneliness (very often/often, *n* (%))	-	1,660 (1.6%)
Incident depression		
Cases (*n*, %)	-	1,915 (1.5%)
Follow-up time, years (mean, SD)	-	8.4 (5.4)
Incident anxiety		
Cases (*n*, %)	-	1,626 (1.2%)
Follow-up time, years (mean, SD)	-	8.4 (5.4)
Incident cerebrovascular disease		
Cases (*n*, %)	-	799 (0.6%)
Follow-up time, years (mean, SD)	-	8.4 (5.4)

BMI, body mass index; SD, standard deviation.

High estCRF in late adolescence was associated with a significantly lower risk for all outcomes (Table 2). In the fully adjusted model, higher estCRF was associated with lower risk for incident depression (HR=0.79, 95% CI: 0.69−0.89) and incident anxiety (HR=0.79, 95% CI: 0.68−0.90), however not significantly associated with incident cerebrovascular disease (HR=0.85, 95% CI 0.68−1.05). Higher estCRF in adulthood was also associated with a significantly lower risk for incident anxiety (HR=0.90, 95% CI: 0.83−0.98) in fully adjusted models. Incident depression and incident cerebrovascular disease were not statistically significantly associated with higher estCRF; however, there was a trend toward a small protective effect (HR=0.94, 95% CI: 0.87−1.01 and HR=0.90, 95% CI 0.79−1.01, respectively) (Table 2).

Spline regression models showed a similar pattern in the association between change in estCRF and the risk of the three outcomes (Figure 1). An increase in z-score, L/min, as well as mL/min/kg between assessments was associated with lower risk and a decrease in relative and absolute estCRF with a higher risk for incident depression (Model 4: $p<0.01$, $p=0.04$, and $p=0.03$, respectively), incident anxiety (Model 4: $p<0.01$, $p=0.167$, and $p=0.02$, respectively), and incident cerebrovascular disease (Model 4: $p=0.09$, $p=0.04$, and $p=0.02$, respectively), see Figure 1. Adjustment for confounders only marginally changed the associations, except for incident cerebrovascular disease, where adjustment for age at adulthood assessment changed the association from the crude model.

Table 3 analyzed change in estCRF categories with the three outcomes. Compared to those who stayed in the moderate or high estCRF category at both time points, decreasing from the moderate or high to the low category was associated with higher risk for both incident depression (HR=1.24, 95% CI 1.07−1.45) and incident anxiety (HR=1.25, 95% CI 1.06−1.49). Those increasing from moderate to high estCRF, compared to those in the constant moderate or high category, had a decreased risk of incident anxiety (HR=0.84, 95% CI 0.71−0.99). Simultaneously, staying in the constant low category at both time points was borderline associated with increased risk of incident anxiety (HR=1.30, 95% CI 0.99−1.71, $p=0.051$); for more details, see Table 3. Change in estCRF was not significantly associated with cerebrovascular disease.

In a sensitivity analysis to address indicators of the magnitude of reverse causality, cases during the first 2 years of follow-up were excluded. The results displayed very similar effect sizes for estCRF measured in early adulthood and at adulthood with later incident depression, incident anxiety, and incident cerebrovascular disease. In the model with incident cerebrovascular disease,

Table 2. Association Between estCRF at Late Adolescence and in Adulthood With Incident Depression, Anxiety, and Cerebrovascular Disease

Outcomes	Late adolescence				Adulthood			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]	Model 7[g]	Model 8[h]
Depression *HR (95% CI)*	**0.61 (0.54; 0.69)**	**0.66 (0.59; 0.74)**	**0.74 (0.65; 0.83)**	**0.79 (0.69; 0.89)**	**0.85 (0.79; 0.90)**	**0.80 (0.76; 0.86)**	**0.89 (0.83; 0.96)**	0.94 (0.87; 1.01)
p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**	0.110
Anxiety *HR (95% CI)*	**0.59 (0.52; 0.67)**	**0.65 (0.58; 0.74)**	**0.74 (0.65; 0.84)**	**0.79 (0.68; 0.90)**	**0.87 (0.81; 0.93)**	**0.79 (0.74; 0.85)**	**0.88 (0.81; 0.94)**	**0.90 (0.83; 0.98)**
p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**	**0.016**
Cerebrovascular disease *HR (95% CI)*	**0.78 (0.65; 0.95)**	**0.77 (0.64; 0.93)**	**0.82 (0.68; 0.99)**	0.85 (0.68; 1.05)	**0.59 (0.53; 0.65)**	**0.85 (0.77; 0.95)**	**0.88 (0.78; 0.98)**	0.90 (0.79; 1.01)
p-value	**<0.001**	**0.007**	**0.040**	0.122	**<0.001**	**0.004**	**0.023**	0.075

Note: Boldface indicates statistical significance ($p<0.05$).
[a]Adjusted for body weight at late adolescence.
[b]Adjusted for Model 1 and year, age, and BMI at late adolescence, as well as conscription test site.
[c]Adjusted for Model 2 and IQ at late adolescence and lifetime somatic and psychiatric comorbidity.
[d]Adjusted for Model 3 and CRF, stress, loneliness, overall health status, smoking, and weekly exercise, all in adulthood.
[e]Adjusted for body weight in adulthood.
[f]Adjusted for Model 5 and age in adulthood.
[g]Adjusted for Model 6 and CRF at late adolescence, as well as lifetime somatic and psychiatric comorbidity.
[h]adjusted for Model 7 and stress, loneliness, overall health status, smoking, and weekly exercise, all in adulthood.
BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio.

the estimates remained similar however nonsignificant, most likely due to lower power. See Appendix Table 2 for more details.

DISCUSSION

The main findings were threefold in this large sample of men with an assessment of estCRF in late adolescence and adulthood. First, a higher estCRF in both late adolescence and adulthood was associated with a lower risk of incident depression, incident anxiety, and incident cerebrovascular disease later in life, with the association being even more pronounced with estCRF in late adolescence. Secondly, an increase in estCRF between the two assessment time points was associated with lower risk and a decrease in estCRF was associated with a higher risk for all three outcomes. This was regardless of whether change was assessed as relative estCRF (z-score) or absolute estCRF (L/min and mL/min/kg). Third, when categorizing estCRF into low, moderate, and high, results showed that participants decreasing from constant moderate or high estCRF in late adolescence to low estCRF in adulthood had an increased risk of depression and anxiety. Finally, increasing from moderate to high estCRF (compared to staying in the constant moderate or high category) category was associated with a lower risk of anxiety.

The study confirms and extends previous research examining the association between CRF and depression and anxiety, both at one as well as multiple time points.[21,22,24] A systematic review and meta-analysis found low and medium CRF (one-time point) to be associated with 47% and 23% higher risk of common mental health symptoms, compared to high CRF, and more specifically with 64% and 31% higher risk of depression.[8] While the present results confirm this, they also extend the knowledge by using exercise-based tests for CRF, including a large population, and physician-confirmed diagnoses of the outcomes from the registries. Further, the results align with studies measuring CRF at more than one-time point. Dishman et al.[22] found males to have increased odds of depression with a decline in CRF. Measuring CRF at multiple time points is aligned with the dynamic nature of depression and anxiety from a life-course perspective, and this study, therefore, adds insight into the complex relationship between the exposure and the outcomes studied. Moreover, the association between higher CRF and cerebrovascular disease also aligns with previous studies.[15–17] The results confirm a decreased risk of incident cerebrovascular disease (stroke and vascular dementia) with higher CRF at one-time point,[15,16] and higher or stable CRF between the two assessment points.[17] Further, a decline in CRF has

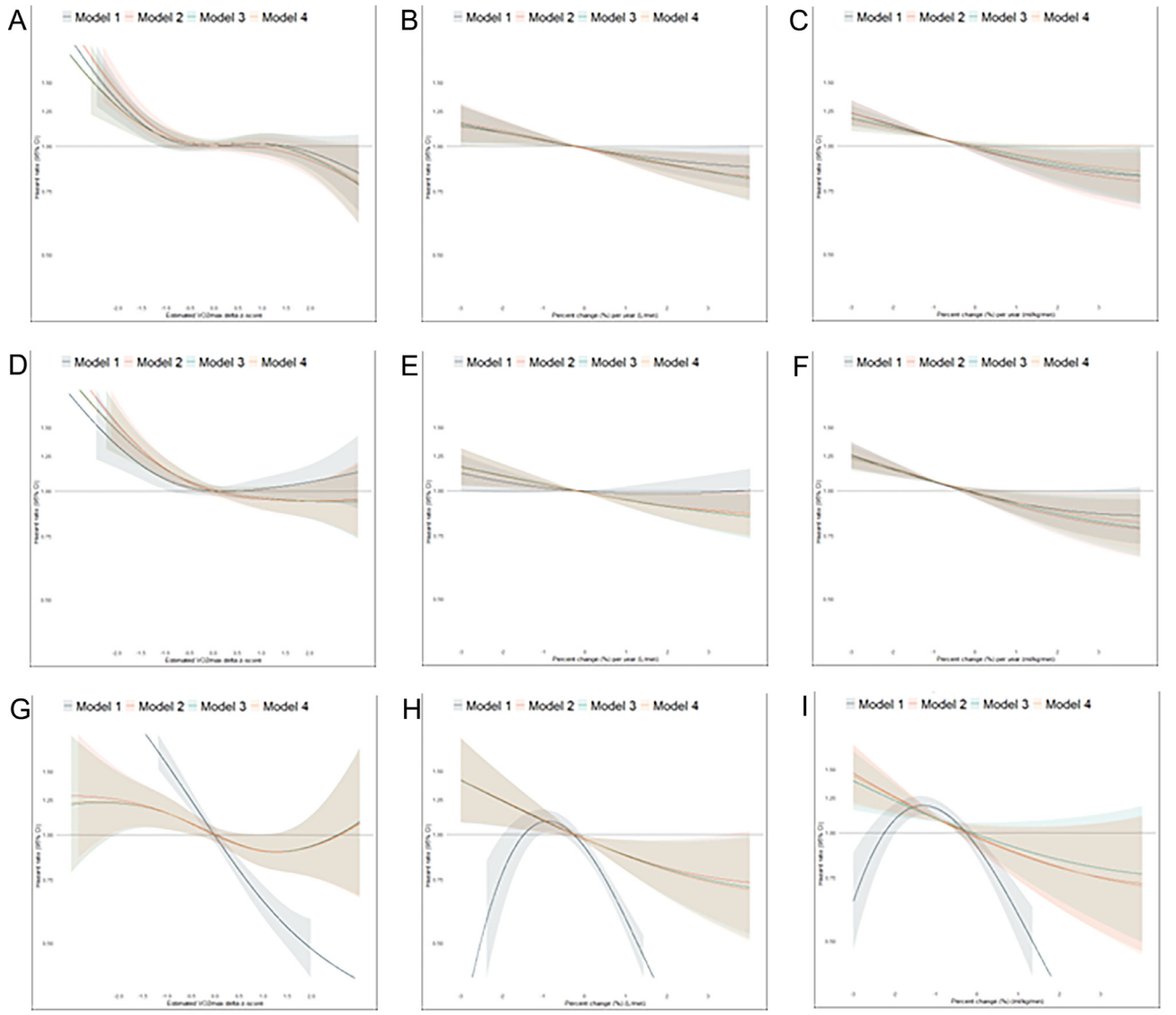

Figure 1. (A–I) Association between estCRF change, between late adolescence and adulthood, and the three outcomes. Cox regression with restricted cubic splines (Hazard ratio, 95% CI), knots at 5th, 50th, and 95th percentile for all, with 50th percentile as reference. (A) Association between depression and change in relative estCRF (delta z-score). (B) Association between depression and annual percent change in estCRF (L/min). (C) Association between depression and annual percent change in estCRF (mL/min/kg). (D) Association between anxiety and change in relative estCRF (delta z-score). (E) Association between anxiety and annual percent change in estCRF (L/min). (F) Association between anxiety and annual percent change in estCRF (mL/min/kg). (G) Association between cerebrovascular disease and change in relative estCRF (delta z-score). (H) Association between cerebrovascular disease and annual percent change in estCRF (L/min). (I) Association between cerebrovascular disease and annual percent change in estCRF (mL/min/kg). Model 1; crude. Model 2; adjusted for age and CRF at conscription. Model 3; additionally adjusted for somatic and psychiatric comorbidity. Model 4; additionally adjusted for BMI at conscription. BMI, body mass index; CRF, cardiorespiratory fitness; HPA, Health Profile Assessment.

also been found to be associated with other poor health outcomes, such as high blood pressure and poor self-rated health.[25,26] Maintaining or increasing CRF throughout life can be seen as a protective factor and prevention priority against many aspects of ill health.

There are several potential mechanisms suggested to explain the associations between CRF and depression and anxiety. In previous research, exercise and CRF changes have been associated with structural, cellular, and molecular changes in the brain that promote functioning in brain regions involved in mental health disorders[34,35]; one example is the hippocampus.[36–38] Another plausible explanation is that exercise and change in CRF can reduce inflammation and increase

Table 3. Association Between Change in estCRF Category Between the Two Assessments and the Three Outcomes

estCRF category	Depression			Anxiety			Cerebrovascular disease		
	Cases/total	*HR (95% CI)*	*p-value*	*Cases*	*HR (95% CI)*	*p-value*	*Cases*	*HR (95% CI)*	*p-value*
Constant moderate or high	994/71,242	Ref		859	Ref		431	Ref	
Increasing (from moderate to high)	219/14,296	0.97 (0.84; 1.13)	0.689	184	**0.84 (0.71; 0.99)**	**0.035**	46	0.78 (0.57; 1.06)	0.111
Increasing (from low to moderate/high)	234/14,767	1.15 (0.99; 1.34)	0.065	202	1.14 (0.97; 1.34)	0.111	86	1.13 (0.88; 1.46)	0.330
Decreasing (from high to moderate)	179/15,055	0.92 (0.78; 1.08)	0.312	154	0.92 (0.77; 1.09)	0.337	77	0.88 (0.69; 1.12)	0.295
Decreasing (from high/moderate to low)	215/15,852	**1.24 (1.07; 1.45)**	**0.005**	166	**1.25 (1.06; 1.49)**	**0.010**	120	1.05 (0.85; 1.29)	0.673
Constant low	75/5,559	1.18 (0.92; 1.51)	0.182	62	1.30 (0.99; 1.71)	0.051	40	1.00 (0.71; 1.43)	0.988

Note: Boldface indicates statistical significance ($p<0.05$). The models are adjusted for BMI and site at conscription, age in adulthood, and lifetime somatic and psychiatric comorbidity.
BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio.

resistance to damage from oxidative stress,[39–43] which in turn also have been linked to the pathophysiology of mental health disorders, including depression and anxiety.[44–47]

Studies on CRF in the context of cerebrovascular conditions are scarce; however, in some studies,[48–50] but not all,[51] physical activity has been linked to decreased risk of cerebrovascular disease. Physical activity may act as a protective factor against cerebrovascular disease by preserving neural plasticity[52] and hippocampal volume.[53,54] An alternative mechanism may also be lowering the risk of cardiovascular diseases,[49] thereby reducing the risk of cerebrovascular disease.

Limitations

Some limitations are important to consider when interpreting this study's results. Although participation in the conscription register is population-based and nationwide in Sweden during the included years, the study included only those with a valid CRF test. Those lacking CRF testing are likelier to have a low CRF score, and this selection bias may, therefore underestimate the associations between low CRF and the outcome.[55] Participation in the adulthood assessment is voluntary and includes only employed people, which further limits the findings' generalizability. Furthermore, the submaximal tests only estimate $\dot{V}O_2$max. Although CRF estimated from the protocols used in late adolescence and adulthood have shown moderate to high validity compared to directly measured $\dot{V}O_2$max,[32,56,57] protocols that estimate actual CRF provides less precise measure of CRF. In turn, less precise measures often lead to a weaker, and underestimated, association with any outcome studied. The significant genetic contribution of CRF level and risk of the three outcomes must also be considered when interpreting the results. A change in CRF level may depend on both genetic factors and changes in moderate-to-vigorous physical activity. Even though the study includes a large sample size, a relatively small number of incident cases are included, especially cerebrovascular disease. This may have been due to the relatively short follow-up period, the young age group included, or that individuals who had received a diagnosis of depression, anxiety, stroke, and/or cerebrovascular disease before the CRF test in adulthood were excluded. The low incidence in the study could lead to underestimating the investigated associations. Although age at follow-up was adjusted for in the analyses, this should be considered when interpreting the results. Finally, as only men are included in this study, it is unclear how the results can be generalized for women, and future research should focus on also including women.

CONCLUSIONS

The findings indicate that there is a longitudinal association between change in CRF and the risk of depression, anxiety, and cerebrovascular disease later in life. Preserving a constant (moderate or high) CRF or increasing ones CRF throughout life can be considered part of a long-term strategy to reduce the risk of these disorders. Furthermore, a decrease in CRF can be a useful indicator for identifying and preventing the risk of developing these disorders at a population level.

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HPI Health Profile Institute manages the HPA database and has also been responsible for the standardization of methods and education of HPA coaches and for developing software for collecting the data used in the study. Representatives from all funding companies have been invited to have their intellectual input on the findings based on their expertise.

Conflict of interest: Sofia Paulsson is employed by the HPI Health Profile Institute, which has provided the data used in the study. All other authors reported no financial disclosures.

CREDIT AUTHOR STATEMENT

Camilla A. Wiklund: Conceptualization, Data curation, Formal analysis, Writing — original draft, Writing — review & editing. Magnus Lindwall: Conceptualization, Writing — review & editing. Örjan Ekblom: Conceptualization, Methodology, Writing — review & editing. Jenny Nyberg: Writing — review & editing. Maria I Åberg: Writing — review & editing. Sofia Paulsson: Resources, Writing — review & editing. Elin Ekblom-Bak: Conceptualization, Methodology, Writing — review & editing, Supervision.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2024.07.012.

REFERENCES

1. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol.* 2017;32(5):541–556. https://doi.org/10.1097/hco.0000000000000437.
2. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci.* 2015;17(3):327–335. https://doi.org/10.31887/DCNS.2015.17.3/bbandelow.
3. World Health Organization. (2023). Depressive disorder (depression) [Fact sheet]. https://www.who.int/news-room/fact-sheets/detail/depression. Accessed January 26, 2024.
4. Hakim AM. Depression, strokes and dementia: new biological insights into an unfortunate pathway. *Cardiovasc Psychiatry Neurol.* 2011;2011:649629. https://doi.org/10.1155/2011/649629.
5. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *Br J Psychiatry.* 2016;208(3):223–231. https://doi.org/10.1192/bjp.bp.114.156554.
6. Mitchell JH, Raven PB. Cardiovascular adaptation to physical activity. In: Bouchard C, Shepard RJ, Stephens T, eds. Physical Activity, Fitness and Health: International Proceedings and Consensus Statement. Human Kinetics Publishers Inc, 1994:286–301.
7. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc.* 2001;33(6 suppl):S446–S451 discussion S452-3. https://doi.org/10.1097/00005768-200106001-00013.
8. Kandola A, Ashdown-Franks G, Stubbs B, Osborn DPJ, Hayes JF. The association between cardiorespiratory fitness and the incidence of common mental health disorders: a systematic review and meta-analysis. *J Affect Disord.* 2019;257:748–757. https://doi.org/10.1016/j.jad.2019.07.088.
9. Kandola AA, Osborn DPJ, Stubbs B, Choi KW, Hayes JF. Individual and combined associations between cardiorespiratory fitness and grip strength with common mental disorders: a prospective cohort study in the UK Biobank. *BMC Med.* 2020;18(1):303. https://doi.org/10.1186/s12916-020-01782-9.
10. Schuch FB, Vancampfort D, Sui X, et al. Are lower levels of cardiorespiratory fitness associated with incident depression? A systematic review of prospective cohort studies. *Prev Med.* 2016;93:159–165. https://doi.org/10.1016/j.ypmed.2016.10.011.
11. Nyberg J, Henriksson M, Åberg MAI, et al. Cardiovascular fitness in late adolescent males and later risk of serious non-affective mental disorders: a prospective, population-based study. *Psychol Med.* 2018;48(3):416–425. https://doi.org/10.1017/s0033291717001763.
12. 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. https://doi.org/10.1192/bjp.bp.111.103416.
13. Willis BL, Leonard D, Barlow CE, Martin SB, DeFina LF, Trivedi MH. Association of midlife cardiorespiratory fitness with incident depression and cardiovascular death after depression in later life. *JAMA Psychiatry.* 2018;75(9):911–917. https://doi.org/10.1001/jamapsychiatry.2018.1467.
14. Åberg ND, Kuhn HG, Nyberg J, et al. Influence of cardiovascular fitness and muscle strength in early adulthood on long-term risk of stroke in Swedish men. *Stroke.* 2015;46(7):1769–1776. https://doi.org/10.1161/strokeaha.115.009008.
15. Hörder H, Johansson L, Guo X, et al. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. *Neurology.* 2018;90(15):e1298–e1305. https://doi.org/10.1212/wnl.0000000000005290.
16. Kulmala J, Solomon A, Kåreholt I, et al. Association between mid- to late life physical fitness and dementia: evidence from the CAIDE study. *J Intern Med.* 2014;276(3):296–307. https://doi.org/10.1111/joim.12202.
17. Prestgaard E, Mariampillai J, Engeseth K, et al. Change in cardiorespiratory fitness and risk of stroke and death: long-term follow-up of healthy middle-aged men. *Stroke.* 2019;50(1):155–161. https://doi.org/10.1161/strokeaha.118.021798.
18. Nyberg J, Åberg MA, Schiöler L, et al. Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia. *Brain.* 2014;137(Pt 5):1514–1523. https://doi.org/10.1093/brain/awu041.
19. Defina LF, Willis BL, Radford NB, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort

study. *Ann Intern Med.* 2013;158(3):162–168. https://doi.org/10.7326/0003-4819-158-3-201302050-00005.
20. Rahman MS, Helgadóttir B, Hallgren M, et al. Cardiorespiratory fitness and response to exercise treatment in depression. *BJPsych Open.* 2018;4(5):346–351. https://doi.org/10.1192/bjo.2018.45.
21. Henriksson P, Henriksson H, Tynelius P, et al. Fitness and body mass index during adolescence and disability later in life: a cohort study. *Ann Intern Med.* 2019;170(4):230–239. https://doi.org/10.7326/m18-1861.
22. Dishman RK, Sui X, Church TS, Hand GA, Trivedi MH, Blair SN. Decline in cardiorespiratory fitness and odds of incident depression. *Am J Prev Med.* 2012;43(4):361–368. https://doi.org/10.1016/j.amepre.2012.06.011.
23. Carlsen T, Salvesen Ø, Sui X, et al. Long-term changes in depressive symptoms and estimated cardiorespiratory fitness and risk of all-cause mortality: the Nord-Trøndelag health study. *Mayo Clin Proc.* 2018;93(8):1054–1064. https://doi.org/10.1016/j.mayocp.2018.01.015.
24. Zotcheva E, Pintzka CWS, Salvesen Ø, Selbæk G, Håberg AK, Ernstsen L. Associations of changes in cardiorespiratory fitness and symptoms of anxiety and depression with brain volumes: the HUNT study. *Front Behav Neurosci.* 2019;13:53. https://doi.org/10.3389/fnbeh.2019.00053.
25. Holmlund T, Blom V, Hemmingsson E, et al. Change in cardiorespiratory fitness on self-rated health: prospective cohort study in 98 718 Swedish adults. *Scand J Public Health.* 2023;51(4):542–551. https://doi.org/10.1177/14034948211047140.
26. Holmlund T, Ekblom B, Börjesson M, Andersson G, Wallin P, Ekblom-Bak E. Association between change in cardiorespiratory fitness and incident hypertension in Swedish adults. *Eur J Prev Cardiol.* 2021;28(13):1515–1522. https://doi.org/10.1177/2047487320942997.
27. Tari AR, Nauman J, Zisko N, et al. Temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality: a population-based prospective cohort study. *Lancet Public Health.* 2019;4(11):e565–e574. https://doi.org/10.1016/s2468-2667(19)30183-5.
28. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;24(11):659–667. https://doi.org/10.1007/s10654-009-9350-y.
29. Ludvigsson JF, Berglind D, Sundquist K, Sundström J, Tynelius P, Neovius M. The Swedish military conscription register: opportunities for its use in medical research. *Eur J Epidemiol.* 2022;37(7):767–777. https://doi.org/10.1007/s10654-022-00887-0.
30. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol.* 1954;7(2):218–221. https://doi.org/10.1152/jappl.1954.7.2.218.
31. Astrand I. Aerobic work capacity in men and women with special reference to age. *Thesis*. Karolinska Institutet; 1960.
32. Ekblom B, Engström LM, Ekblom O. Secular trends of physical fitness in Swedish adults. *Scand J Med Sci Sports.* 2007;17(3):267–273. https://doi.org/10.1111/j.1600-0838.2006.00531.x.
33. *R: a language and environment for statistical computing.* R Foundation for Statistical Computing; 2021. https://www.R-project.org/
34. Gujral S, Aizenstein H, Reynolds CF 3rd, Butters MA, Erickson KI. Exercise effects on depression: possible neural mechanisms. *Gen Hosp Psychiatry.* 2017;49:2–10. https://doi.org/10.1016/j.genhosppsych.2017.04.012.
35. Kandola A, Hendrikse J, Lucassen PJ, Yücel M. Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: practical implications for mental health treatment. *Front Hum Neurosci.* 2016;10:373. https://doi.org/10.3389/fnhum.2016.00373.
36. Firth J, Stubbs B, Vancampfort D, et al. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. *Neuroimage.* 2018;166:230–238. https://doi.org/10.1016/j.neuroimage.2017.11.007.
37. Li MY, Huang MM, Li SZ, Tao J, Zheng GH, Chen LD. The effects of aerobic exercise on the structure and function of DMN-related brain regions: a systematic review. *Int J Neurosci.* 2017;127(7):634–649. https://doi.org/10.1080/00207454.2016.1212855.
38. Zheng G, Ye B, Zheng Y, et al. The effects of exercise on the structure of cognitive related brain regions: a meta-analysis of functional neuroimaging data. *Int J Neurosci.* 2019;129(4):406–415. https://doi.org/10.1080/00207454.2018.1508135.
39. de Sousa CV, Sales MM, Rosa TS, Lewis JE, de Andrade RV, Simões HG. The antioxidant effect of exercise: a systematic review and meta-analysis. *Sports Med.* 2017;47(2):277–293. https://doi.org/10.1007/s40279-016-0566-1.
40. Eyre HA, Papps E, Baune BT. Treating depression and depression-like behavior with physical activity: an immune perspective. *Front Psychiatry.* 2013;4:3. https://doi.org/10.3389/fpsyt.2013.00003.
41. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol.* 2011;11(9):607–615. https://doi.org/10.1038/nri3041.
42. Lavie CJ, Church TS, Milani RV, Earnest CP. Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. *J Cardiopulm Rehabil Prev.* 2011;31(3):137–145. https://doi.org/10.1097/HCR.0b013e3182122827.
43. Palmefors H, DuttaRoy S, Rundqvist B, Börjesson M. The effect of physical activity or exercise on key biomarkers in atherosclerosis—a systematic review. *Atherosclerosis.* 2014;235(1):150–161. https://doi.org/10.1016/j.atherosclerosis.2014.04.026.
44. Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BW. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology.* 2015;51:164–175. https://doi.org/10.1016/j.psyneuen.2014.09.025.
45. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry.* 2015;172(11):1075–1091. https://doi.org/10.1176/appi.ajp.2015.15020152.
46. Köhler CA, Freitas TH, Maes M, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand.* 2017;135(5):373–387. https://doi.org/10.1111/acps.12698.
47. Moylan S, Eyre HA, Maes M, Baune BT, Jacka FN, Berk M. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours. *Neurosci Biobehav Rev.* 2013;37(4):573–584. https://doi.org/10.1016/j.neubiorev.2013.02.003.
48. Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case-control studies. *Br J Sports Med.* 2022;56(12):701–709. https://doi.org/10.1136/bjsports-2021-104981.
49. Kraus WE, Powell KE, Haskell WL, et al. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc.* 2019;51(6):1270–1281. https://doi.org/10.1249/mss.0000000000001939.
50. Zhu J, Ge F, Zeng Y, et al. Physical and mental activity, disease susceptibility, and risk of dementia: a prospective cohort study based on UK Biobank. *Neurology.* 2022;99(8):e799–e813. https://doi.org/10.1212/wnl.0000000000200701.
51. Bahls M, Leitzmann MF, Karch A, et al. Physical activity, sedentary behavior and risk of coronary artery disease, myocardial infarction and ischemic stroke: a two-sample Mendelian randomization study. *Clin Res Cardiol.* 2021;110(10):1564–1573. https://doi.org/10.1007/s00392-021-01846-7.
52. Gholamnezhad Z, Boskabady MH, Jahangiri Z. Exercise and dementia. *Adv Exp Med Biol.* 2020;1228:303–315. https://doi.org/10.1007/978-981-15-1792-1_20.

53. Erickson KI, Prakash RS, Voss MW, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus.* 2009;19 (10):1030–1039. https://doi.org/10.1002/hipo.20547.
54. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA.* 2011;108(7):3017–3022. https://doi.org/10.1073/pnas.1015950108.
55. Af Geijerstam A, Mehlig K, Börjesson M, et al. Fitness, strength and severity of COVID-19: a prospective register study of 1 559 187 Swedish conscripts. *BMJ Open.* 2021;11(7):e051316. https://doi.org/10.1136/bmjopen-2021-051316.
56. Andersen LB. A maximal cycle exercise protocol to predict maximal oxygen uptake. *Scand J Med Sci Sports.* 1995;5(3):143–146. https://doi.org/10.1111/j.1600-0838.1995.tb00027.x.
57. Björkman F, Ekblom-Bak E, Ekblom Ö, Ekblom B. Validity of the revised Ekblom Bak cycle ergometer test in adults. *Eur J Appl Physiol.* 2016;116(9):1627–1638. https://doi.org/10.1007/s00421-016-3412-0.