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Research Article

Incremental Increases in Non-Exercise Estimated Fitness Reduce Subsequent Depressive Symptoms

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Abstract

The purpose of this observational retrospective cohort study was to examine the association between non-exercise estimated Cardiorespiratory Fitness (eCRF) and incident depressive symptoms. A total of 14,431 participants from the Aerobics Center Longitudinal Study cohort between February 5, 1979 and December 31, 1998, were followed for incident depressive symptoms through December 31, 1999. Depressive symptoms were determined by the CES-D 10 item questionnaire. eCRF in MET was determined from a non-exercise algorithm developed by Jackson and further grouped into sex-specific tertiles. Multivariable logistic regression was used to estimate odds ratios and 95% confidence intervals. 11.7% of men and 14.8% of women developed depressive symptoms after a mean of 12 follow- up years. In the overall sample, the odds ratio of depressive symptoms was 0.84 (95% CI 0.74-0.95) times lower in the middle eCRF tertile than in the lower tertile and was 0.74 (95% CI 0.66-0.85) times lower in the highest tertile. Each 1-MET increase in fitness reduced the odds ratio for depressive symptoms by 0.91 times (95% CI 0.89-0.93). The pattern of the association between eCRF and incident depressive symptoms was consistent between men and women, however, the magnitude of the risk reduction was smaller in women than in men. eCRF is a useful predictor of depressive symptoms. The non-traditional way of estimating CRF might provide more clinical utility compared to CRF measured using standard exercise protocols.

Keywords: Fitness; Depression; Cohort Study

Introduction

Cardiorespiratory Fitness (CRF) is the coordination of anatomy with physiology to use oxygen to sustain physical activity and is given in Metabolic Equivalents (METs). Ross and others have cited the substantial evidence for the measurement of CRF in clinical practice [1]. The criterion measure of CRF is indirect calorimetry, but the costs, participant burden and invasiveness make exercise testing a more practical measure. The practicality of exercise testing is limited by resources and the participant burden. While not an alternative for objective assessment of CRF, non-exercise estimated CRF (eCRF) may provide reasonably accurate estimates of CRF which could be a valid alternative in risk assessment [1-5]. We have determined that eCRF estimated by the 2012 Jackson algorithm has a graded association with all-cause mortality, Coronary Heart Disease (CHD), hypertension and cancer, when applied to NHANES III [6-10]. We have also demonstrated that the Jackson algorithm associates with incident stroke differently across race in the REGARDS study which supports the assumption that algorithms are population specific [1,12]. However, we also support the assumption that eCRF is limited but practical when exercise testing is not an option in a 2019 review [13].

We have used a comparable eCRF algorithm to predict depressive symptoms in the Norwegian HUNT study, so it should follow that we anticipate a similar validity for the Jackson model to predict depressive symptoms in a US population [14,15]. It should also follow that the relationship we described in 2009 between incident depressive symptoms and CRF and the relationship between eCRF and incident depressive symptoms that we will describe in the present study are probably reasonably similar in direction and magnitude [16]. Previously, in an Aerobics Center Longitudinal Study cohort of 11,258 men and 3,085 women, after a mean 12 years of follow- up, CRF determined on a maximal treadmill test predicted the incidence of depressive symptoms that for men and women, high CRF (upper 40%) reduced the risk of symptom development by 51% and 54%, respectively, compared to low CRF (lowest 20%) [16]. In this study of a comparable Aerobics Center Longitudinal Study cohort of 14,431 men and women, we examined the relationship of eCRF with incident depressive symptoms under multivariate analysis across the criteria of eCRF.

Material and Methods

Study Design and Participants

We analyzed data from the Aerobics Center Longitudinal Study cohort of men and women examined at the Cooper Clinic in Dallas, TX. The study methods have been reported elsewhere [16,17]. In brief, the study participants came to the clinic for periodic preventive medical examinations and for counseling regarding health and lifestyle behavior factors between 1979 and 1998. Patients came from all 50 states; most were self-referred with some referred by their physicians or employers. At the time of their clinic examination, the Aerobics Center Longitudinal Study was described to patients, who then provided written informed consent. The Cooper Institute Institutional Review Board annually reviewed and approved the study protocol.

All participants had complete data to calculate the non-exercise eCRF. We excluded 666 individuals who met the following criteria: myocardial infarction (n=132), stroke (n=22), cancer (n=271), body mass index (BMI)<18.5 (n=130), age<20 or age>90 (n=111). Those who reported a previously diagnosed mental disorder, such as depression, anxiety, thoughts of suicide, or psychiatric counseling were also excluded from the analysis (n=1398). Among the eligible participants, 14431 individuals completed the 10-item Center for Epidemiological Studies Depression Scale (CES-D 10) during 1990-1999 and therefore became the final analytical sample for the current study.

Assessment of Non-Exercise eCRF

Non-exercise eCRF at baseline was estimated in METs (3.5 mL O2·kg-1·min-1) with the following sex-specific algorithms: eCRF in men (METs) =21.2870 + (0.1654*age) - (0.0023*age2) - (0.2318*BMI) - (0.0337*waist circumference or waist circumference) - (0.0390*resting heart rate) + (0.6351*physically active) - (0.4263*current smoker) eCRF in women (METs) =14.7873 + (0.1159*age) - (0.0017*age2) - (0.1534*BMI) - (0.0085*waist circumference) - (0.0364*resting heart rate) + (0.5987*physically active) - (0.2994*current smoker) [6]. Age, BMI, waist circumference and RHR are entered as continuous variables, whereas physical activity and being a current smoker are dichotomous variables with a value of 1 when present and 0 when absent.

BMI was calculated from measured height and weight in accordance with standard procedures during participants' clinical visit. Waist circumference was measured level with the umbilicus. RHR was determined with the participants recumbent after 5-minute rest before the test and was obtained from the resting ECG [18]. Physical activity was assessed with a five-level physical activity index based on a formerly validated questionnaire [6,19,20]. Physically active was defined as walking or jogging 10 miles or more per week that was equal to the physical activity index levels 3 and 4; inactive was defined as walking or jogging less than 10 miles per week, participating in some other regular physical activity such as bicycling, swimming, racquet sports and other strenuous sports, but not walking or jogging, or no regular physical activity that was equal to the physical activity index levels 0 to 2. Participants also reported their smoking status (never smoked, former smokers, or current smokers). Once the algorithms were implemented, participants were classified into lower, middle and upper groups on the basis of age- (20-30, 40-49, 50-59, or ≥60 years) and sex-specific thirds of the estimated METs distribution.

Measurement of Depressive Symptoms

Depressive symptoms were assessed after the baseline visit using the 10-item Center for Epidemiological Studies Depression Scale (CES-D) questionnaire as part of a mail-back survey in 1990 (n=7664 participants), 1995 (n=7295), or 1999 (n=8984) [21,22]. Some participants responded to more than one survey. For those who completed multiple surveys, we used the last one if they

reported no elevated depressive symptoms and the first one for those who reported elevated depressive symptoms. The CES-D 10 has been validated with good reliability in general populations [11,21,22]. We have used this method to assess depressive symptoms in our previous works [16,17,23]. The aggregate survey response rate was approximately 65% [16,31]. In brief, participants were asked to respond to ten items by providing a 4-point ordinal scale answer from "less than 1 day" to "5-7 days". Eight of the ten CES-D items assessed different aspects of depressed mood, while the remaining two (reverse scored) items assessed a more hopeful, happy mood state. Although the CES-D is a screening measure rather than a diagnostic tool, a score of ≥8 on the CES-D 10 (which corresponds to a cutoff of 16 on the 20-item CES-D) is considered to indicate the presence of elevated depressive symptoms [11].

Potential Confounders

Potential confounding variables included age, marital status, alcohol consumption, hypertension, diabetes and hypercholesterolemia, collected during baseline examinations according to the Cooper Clinic's standardized manual of operations [19]. After an overnight fast of at least 12 hours, an extensive physical examination and preventive health evaluation were performed. The examination included measures of blood pressure, blood for chemistry analyses, personal health history and lifestyle habits. Hypertension was defined as a physician diagnosis, systolic blood pressure ≥140 mm/H g or diastolic blood pressure ≥ 90 mm/Hg. Diabetes mellitus was defined as a physician diagnosis, insulin use, or fasting glucose ≥126 mg/dL. Hypercholesterolemia was defined as a physician diagnosis or total cholesterol ≥240 mg/dL.

Statistical Analysis

Baseline characteristics of the study population were characterized by depressive symptoms status (developed depressive symptoms/did not develop depressive symptoms) in men and women. Differences in covariates were tested using Student t-tests and chi-square tests. Because the exact depressive symptoms development time was uncertain, sex-specific logistic regression models were used to examine the association between non-exercise eCRF and risk of developing depressive symptoms. Odds Ratios (ORs) and 95% confidence intervals (CIs) were reported as an index of the strength of association. Two models were tested: 1) age and survey indicator-adjusted model; 2) multivariable-adjusted model including the following covariates: age (in years), survey indicator, year of baseline examination, marital status (currently married or not), heavy alcohol intake (>14 drinks/week in men, or >7 drinks/week in women) and presence of hypertension, diabetes, or hypercholesterolemia (yes/no for each). To account for differences in survey response patterns among study participants and for the possibility that external events may have differentially affected responses to the CES-D during the three survey periods, we created a dummy variable that indicated whether the outcome measurement was from 1990, 1995 or 1999. We assessed linear trends in the association of non-exercise CRF with the risk of depressive symptoms. We also examined non-exercise CRF as a continuous variable so that each odds ratio represents the risk associated with a 1-MET increase in the exposure variable. We then performed stratified analyses across components of non-exercise eCRF, as follows: age (<45, ≥45), BMI (<median, ≥median), waist circumference (<median, ≥median), resting heart rate (<median, ≥median), physical active (inactive, active) and smoking status (current smoker, nonsmoker). Analyses were conducted in 2021 using SAS, version 9.4, with alpha set at P<.05.

Results

After a mean of 12 years follow up, 11.7% of men and 14.8% of women developed depressive symptoms. Baseline characteristics grouped by sex and depressive symptoms are shown in Table 1. Men who developed depressive symptoms on average were younger, less active, less likely to be married, more likely to be a smoker; had a greater BMI, waist circumference and higher triglycerides; had lower systolic blood pressure and a lower prevalence of hypertension, compared to men who did not develop depressive symptoms. In women, those who developed depressive symptoms had a higher waist circumference, were less likely to be married, less likely to be a heavy drinker and had a higher prevalence of hypercholesterolemia than those who did not develop depressive symptoms.

Table 2 shows the association between eCRF and depressive symptoms. In Model 1, with adjustment for age and survey indicator, an inverse gradient (Ptrend < 0.0001) of depressive symptoms was observed across eCRF groups in the overall sample. After adjustment for covariables, individual with middle and upper eCRF had an 16% (95% CI 0.74 - 0.95) and 26% (95% CI 0.66-0.85) lower odds of depressive symptoms than did those with lower eCRF (Ptrend < 0.0001). Similar inverse patterns of association were observed in men. Compared to men with lower eCRF, the odds of reporting depressive symptoms were 18%

lower in men with middle eCRF and 27% lower in men with higher eCRF. In women, after adjustment for age and survey indicators, those with middle and upper eCRF had a 10% and 24% lower risk of depressive symptoms than did women with lower eCRF (Ptrend=0.05). However, significance was attenuated by adjustment for covariables (Ptrend = 0.09).

Each additional 1-MET increase in baseline eCRF was associated with a 9% reduction in the odds of developing depressive symptoms in the overall sample (OR 0.91, 95% CI 0.89-0.93), a 8% lower odds of developing depressive symptoms in men (OR 0.92, 95% CI 0.89-0.94) and a 12% reduction of the odds in women (OR 0.88, 95% CI 0.82-0.93) after adjusting for age, survey indicator, year of baseline examination, marital status, heavy alcohol intake, presence of hypertension, diabetes and hypercholesterolemia.

Next, we examined whether the dichotomously assessed components of eCRF modified the association between eCRF and depressive symptoms (Fig. 1,2). In men (Fig. 1), both the middle and upper fitness tertiles showed lower odds of developing depressive symptoms across older (Ptrend=0.01) and younger age (Ptrend=0.0005) groups and across higher (Ptrend=0.03) and lower RHR (Ptrend=0.01) groups compared to the lowest eCRF tertile, respectively. There was no significant role of eCRF with odds of developing depressive symptoms when BMI was less than 25. However, when BMI was ≥25 there was a significant inverse trend across the eCRF tertiles (Ptrend=0.003). An inverse trend across eCRF tertiles was observed for both waist circumference strata and physical activity strata, but was only significant in the higher waist circumference group (Ptrend=0.05) and in active men (Ptrend=0.002). Men who were not a current smoker had lower odds of developing depressive symptoms for both upper and middle eCRF tertiles than those in the lower tertile (Ptrend<0.0001).

In women (Fig. 2), the pattern of association between eCRF and depressive symptoms risk was variable across risk factor groups and statistical power often was limited by a small number of events. The only significant inverse trend across eCRF tertiles was observed in those with lower RHR ((Ptrend=0.01).

Characteristic	Men			Women		
	Participants who did not develop depressive symptoms (n=10568)	**Participants who developed depressive symptoms (n=1396)**	**P- value**	**Participants who did not develop depressive symptoms (n=2101)**	**Participants who developed depressive symptoms (n=366)**	**P-value**
Age (yr)	46.1 (9.6)	44.1 (9.0)	<0.0001	45.4 (10.3)	44.5 (10.0)	0.09
Body mass index	25.9 (3.4)	26.3 (3.6)	0.0003	22.6 (3.3)	23.0 (3.6)	0.07
Waist circumference (cm)	92.7 (10.2)	93.5 (10.6)	0.006	71.5 (9.0)	72.9 (9.9)	0.02
Resting heart rate	59 (11)	60 (10)	0.02	63 (10)	64 (11)	0.58
Total cholesterol (mg/dL)	210.2 (39.8)	208.6 (40.6)	0.16	202.1 (48.8)	205.3 (42.9)	0.22
Triglycerides (mg/dL)	127.9 (88.6)	139.5 (45.2)	0.004	89.0 (11.3)	89.8 (55.7)	0.83
Systolic blood pressure (mmHg)	121 (14)	120 (12)	0.002	113 (14)	111 (14)	0.03
Diastolic blood pressure (mmHg)	81 (9)	80 (9)	0.14	76 (9)	75 (9)	0.23
Fasting blood glucose (mg/dL)	100.2 (15.5)	100.3 (19.9)	0.75	98.7 (20.1)	95.3 (14.3)	0.44
Married	31.0	25.8	<0.0001	30.5	20.8	0.0002
Current smoker	12.4	16.1	0.0001	7.6	9.3	0.27
Heavy alcohol drinker*	6.4	6.9	0.52	6.3	3.3	0.02
Physically active†	79.7	75.1	<0.0001	82.1	81.4	0.75
Hypertension‡	29.2	25.9	0.01	14.9	13.9	0.63

Hypercholesterolemia§	19.8	21.2	0.23	14.2	18.3	0.04
Diabetes mellitus#	2.8	3.2	0.51	1.7	2.5	0.29

Data are presented as % or mean (SD).

* Heavy alcohol drinker was defined as drinks per week >14 in male or >7 in female. One drink of alcohol is defined as 12 oz (3.41 dL) of beer, 5 oz (1.421 dL) of wine, or 1.5 oz (0.4262 dL) of hard liquor.

† Physically active was defined as have leisure-time physical activity during the past three months.

‡ Hypertension was defined as a physician diagnosis, systolic blood pressure≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

§Hypercholesterolemia was defined as a physician diagnosis or total cholesterol ≥240 mg/dL

#Diabetes mellitus was defined as a physician diagnosis, insulin use, or fasting glucose ≥126mg/dL.

Table 1: Baseline characteristics of study participants by sex and depressive symptoms during follow-up.

Tertiles of estimated CRF	**N/cases**	**Model 1* OR (95% CI)**	**Model 2† OR (95% CI)**
Men			
T1 (Lower)	3988/532	1.00	1.00
T2 (Middle)	3988/454	0.83 (0.73-0.95)	0.82 (0.71-0.94)
T3 (Upper)	3988/410	0.73 (0.64-0.84)	0.73 (0.64-0.85)
P for linear trend		<0.0001	<0.0001
Per 1-MET increase		0.91 (0.89-0.94)	0.92 (0.89-0.94)
Women			
T1 (Lower)	823/132	1.00	1.00
T2 (Middle)	820/123	0.90 (0.69-1.17)	0.91 (0.69-1.19)
T3 (Upper)	824/111	0.76 (0.58-1.005)	0.78 (0.59-1.04)
P for linear trend		0.05	0.09
Per 1-MET increase		0.86 (0.81-0.91)	0.88 (0.82-0.93)
All			
T1 (Lower)	4811/664	1.00	1.00
T2 (Middle)	4808/577	0.84 (0.75-0.95)	0.84 (0.74-0.95)
T3 (Upper)	4812/521	0.74 (0.65-0.84)	0.74 (0.66-0.85)
P for linear trend		<0.0001	<0.0001
Per 1-MET increase		0.90 (0.88-0.93)	0.91 (0.89-0.93)

*Model 1 adjusted for age and survey indicator from men and women; additional adjusted for gender for all.

†Model 2 adjusted all variables in model 1 plus year of baseline examination, marital status, heavy alcohol intake, presence of hypertension, diabetes, and hypercholesterolemia.

Table 2: Association of estimated Cardiorespiratory Fitness (CRF) and development of depressive symptoms in men and women.

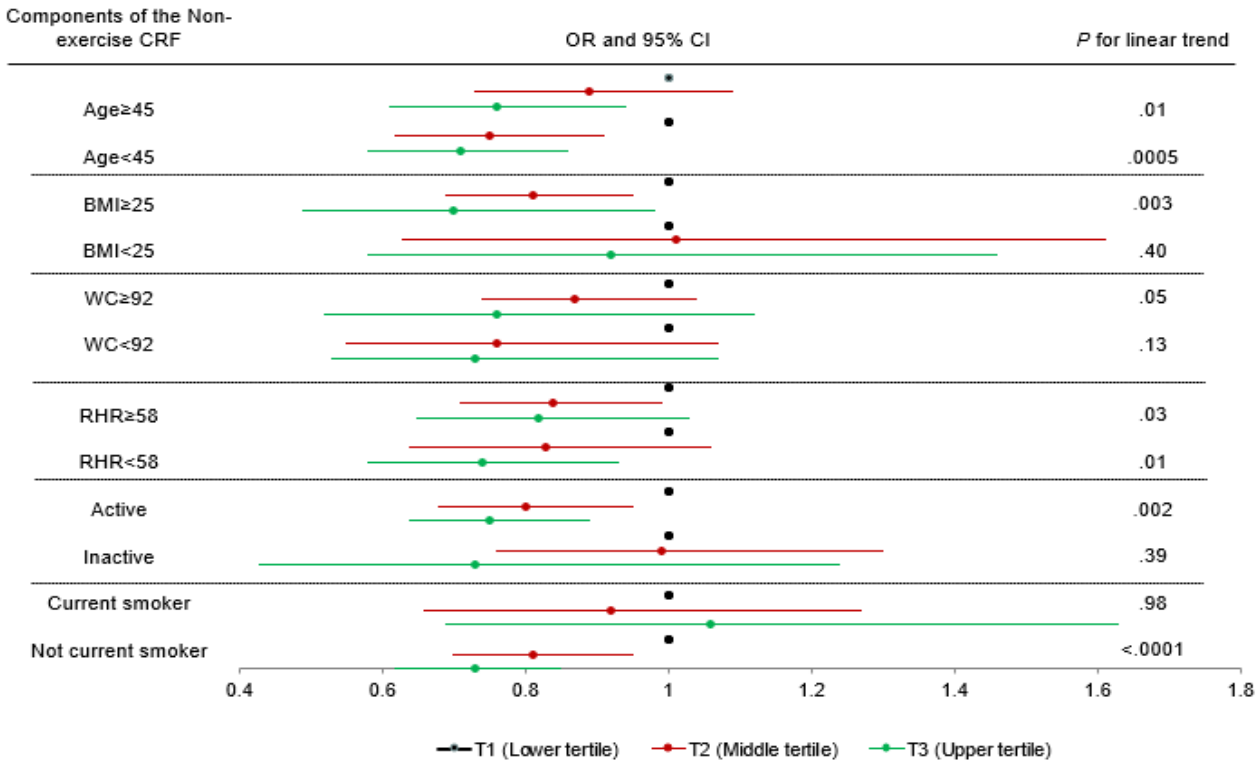

Figure 1: Multivariable*-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of depressive symptoms by tertiles of estimated Cardiorespiratory Fitness (CRF) across strata of the variables in the non-exercise equation in men. *Adjusted by age, year of baseline examination, survey indicator, marital status, heavy alcohol intake, presence of hypertension, diabetes and hypercholesterolemia. T1 (lower tertile) is the referent.

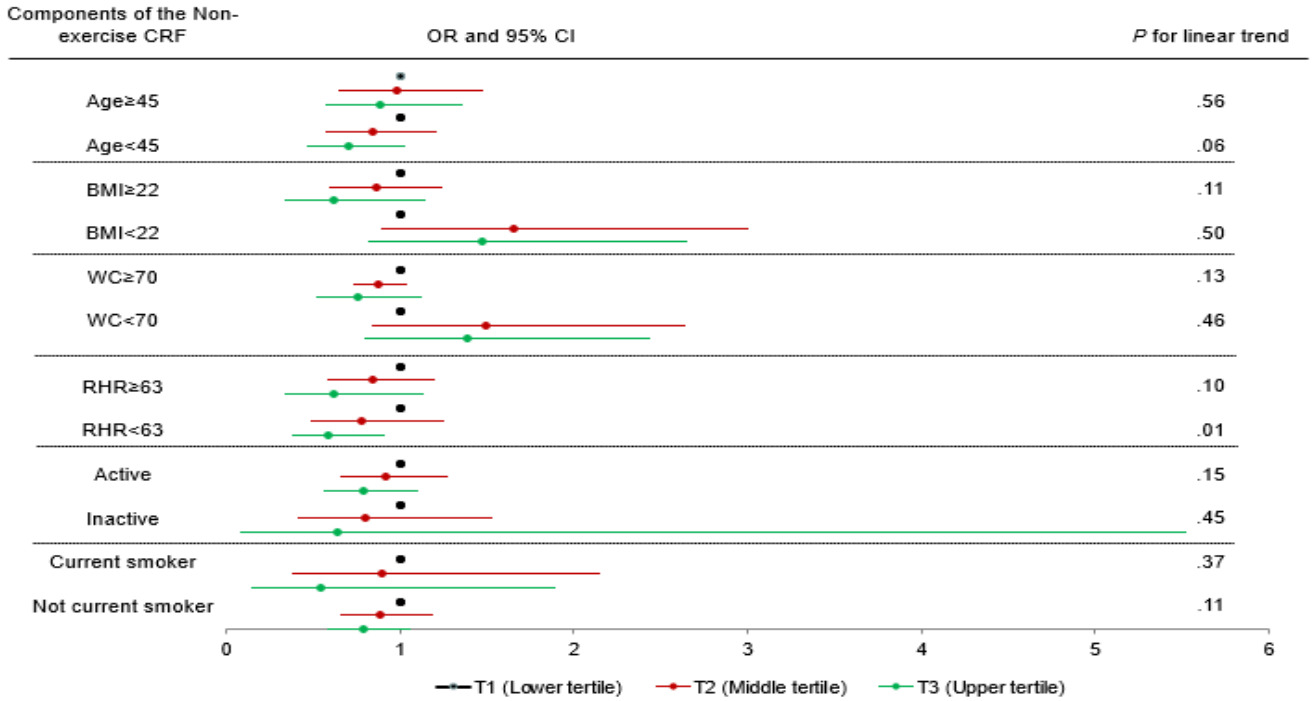

Figure 2: Multivariable*-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of depressive symptoms by tertiles of estimated Cardiorespiratory Fitness (CRF) across strata of the variables in the non-exercise equation in women. *Adjusted by age, year of baseline examination, survey indicator, marital status, heavy alcohol intake, presence of hypertension, diabetes and hypercholesterolemia. T1 (lower tertile) is the referent.

Discussion

eCRF demonstrated a graded inverse association with incident depressive symptoms in a large Aerobics Center Longitudinal Study cohort. Upper and middle eCRF groups experienced a 26% and 16% lower incidence of depression, respectively compared to lower eCRF groups. There was an overall 9% risk reduction per 1-MET increase in eCRF, consistent with our 2019 publication that demonstrated a 22% and 19% lower risk for incident depressive symptoms for high and middle fitness tertiles compared to lower fitness, respectively, and an 11% risk reduction per 1-MET increase in eCRF [15]. It also followed that the risk reduction of eCRF on depressive symptoms agreed with the direction of our 2009 study, but the magnitude of risk reduction was more than halved compared to CRF determined by exercise testing [16]. Objectively-determined CRF was associated with subsequent depression in a recent meta-analysis and systematic review such that the risk for depression estimated to be 19-24% lower for medium CRF and 39-43% lower for high CRF, compared to low CRF [24,25]. The inverse dose-response relationship reported in the current study is largely consistent with the results of previous related works.

The inverse association between eCRF and incident depressive symptoms generally was consistent in strata of the five components of non-exercise eCRF. The prognostic value of eCRF is particularly noteworthy in men who were overweight or obese, or had higher waist girth, who were physically active, or were not current smokers at baseline. Stratified analyses were mostly non-significant in women; however, greater level of eCRF tended to be associated with lower risk of depressive symptoms across the five components of non-exercise CRF. The statistical significance of these cross-tabulations in women was limited by the small number of events, but the prevalence of depression in women is double that of men in the US, which is likely to explain the borderline significant findings in women [26]. Collectively, the present results suggest that eCRF is an important prognostic factor for depressive symptoms in men. Higher eCRF is protective against depressive symptoms across subgroups of age, BMI, waist circumference, resting heart rate, physical activity or smoking status. Assessing eCRF in women is likely of similar benefit to depression risk assessment as in men [14-16,]. However, additional data are needed to confirm the suggestive findings reported here. With a larger sample size of women, we would expect that the inverse association between eCRF and risk of depressive symptoms will likely be comparable to the magnitude of the risk reduction as previously reported [15,16].

Although our study was performed in a primary prevention cohort, substantial data suggest that physical activity and CRF play major roles in secondary CHD prevention and that higher CRF is associated with lower prevalence of depression and better survival in CHD and heart failure cohorts [27-30,33]. Therefore, efforts to improve CRF and reduce depression are especially important in secondary prevention; in patients with established cardiovascular diseases eCRF could offer high clinical utility [8].

One of the main limitations in our study is the relatively small number of women, which leads to lower power for most of the stratified analyses, although men appeared to have an 8% reduction in depression for every 1-MET increase in eCRF, whereas this was 12% in women. Participants in the current study were primarily white and well-educated and had middle to upper socioeconomic status, and the homogeneity of our sample strengthens the internal validity of our findings by reducing potential confounding by unmeasured factors related to socioeconomic status, such as income or education. We did not have sufficient information on medication usage, menopausal status, or dietary habits to include them in our analyses, and it is possible that residual confounding by these factors may exist, although it seems unlikely that it would account for all of the observed association between eCRF and depressive symptoms. In addition, baseline eCRF and other confounders might change during the follow-up period, which might influence the study findings. Lastly, the non-exercise equation was chosen based on our previous work, therefore, we do not know if the key findings might be influenced by CRF estimated from other non-exercise equations. Future longitudinal studies with larger samples of women, more diverse population, eCRF produced from other non-exercise equations and repetitive measures are warranted to provide a better picture of the relationship between eCRF and depressive symptoms.

The measurement of CRF through exercise testing, using gas exchange or based on treadmill time, speed and elevations and standard algorithms has been the traditional route of determination. This study demonstrates that eCRF estimated though a non-exercise equation predicts subsequent depressive symptoms. The consistency of our results with others suggests that eCRF has utility in clinical surveillance when exercise testing is not viable.

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Conflict of Interest
The authors have no conflict of interest to declare.

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