

depression, functional fitness, and ADL after the intervention. We propose using dual-task resistance exercises for cognitive and physical health management in the older adults with cognitive impairment.

**Trial registration** This study was registered with the Clinical Research Information Service (WHO International Clinical Trials Registry Platform) (Registration ID, KCT0005389; Registration date, 09/09/2020).

**Keywords** Dual-task resistance exercise, Resistant exercise, Cognitive impairment, Cognition, Mood, Functional fitness, Activities of daily living

## Introduction

The global aging phenomenon, an indispensable topic in modern society, has sharply increased interest in the lives of the older adult population. Therefore, unlike in ancient times when geriatric diseases were considered natural phenomena, maintaining and improving a healthy body has become a significant social concern [1]. According to a report released by the United Nations in 2020, the number of people aged 65 and over globally is estimated to be 728 million and is expected to reach 1.5 billion by 2050 [2]. In addition, the U.S. Centers for Disease Control and Prevention (2019) reported that 11.7% of adults over the age of 65 suffer from cognitive impairment [3]. Aging is associated with cognitive impairment and contributes to a decline in physical function [4, 5]. Decline in cognitive and physical function can reduce activities of daily life (ADL), leading to feelings of loneliness, alienation, and psychological atrophy, leading to an increase in depression in older adults [6–8]. Decreased physical functions may increase the risk and fear of falls, the incidence of geriatric diseases, and lead to a decrease in self-confidence in performing ADL [9, 10].

Physical exercise is considered an essential healthcare option for older people [11]. Regular exercise can have positive cognitive and physical effects, such as delaying aging-induced neurodegeneration and reducing the risk of falls and depression in older adults [12, 13]. Therefore, various studies are being conducted to improve older adults' cognitive and physical functions. Resistance exercise is mainly used to prevent deterioration of physical functions due to aging [14]. Various literatures have also reported that resistance exercise helps to improve cognitive function by causing structural and functional changes in the brain [15–18].

Dual-task exercise program that combines cognitive training and physical activity programs for older adults with mild cognitive impairment has been reported [19]. Recent studies have also reported that dual-task training improved balance and gait function in patients with stroke [20] and spatio-temporal parameters of gait in older women with dementia [21]. A previous study has reported that exercises that include dual-task could be the key of therapeutic success to slow down the progression of dementia, but risk of falls during dual task

performance compared to single task performance was presented in patients with dementia [22]. A recent systematic review suggested a further study on the capability of cognitive-motor dual-tasks related to falls in patients with stroke [23].

Recent research highlights the effectiveness of resistance exercise interventions in improving physical functionality, mood, and alleviating depression among older adults [14–18]. Additionally, previous studies have reported that exercises that applies dual tasks has demonstrated potential in enhancing cognitive capabilities [24–28]. Based on the findings of these previous studies, it is necessary to perform resistance exercise for the comprehensive management of cognition, emotion, depression, and physical health in older adults. Additionally, adopting a dual-task-based approach is crucial as it holds potential for enhancing cognitive function. The appropriate exercise program for managing older adults' health is dual-task resistance exercise, which can deliver all the benefits of resistance exercise while additionally enhancing cognitive function.

Although there are various reports, controversy exists about dual-task interventions for the rehabilitation of patients with cognitive impairment and the efficacy of exercise programs to improve mood, depression, physical function, and ADL, along with improving cognitive function in older adults with cognitive impairment, is still insufficient. A recent systematic review and meta-analysis has reported positive effects of dual-task exercise on cognition and motor function in older adults with cognitive impairment, but several studies included in the systematic review compared experimental groups with control groups such as health education and placebo activities, not active comparators [29]. Studies in which the risk of selection bias existed were also included. Therefore, it is necessary to prepare evidence through methodologically appropriately designed studies to minimize bias.

This study aimed to examine the effects of an exercise program to improve cognition, mood, depression, physical function, and ADL in older adults with cognitive impairment. The experimental group performed a dual-task resistance exercise program aimed at improving cognitive function, and the control group performed

a resistance exercise program. We hypothesized that dual-task resistance exercise would be more effective in improving cognition compared to resistance exercise. Additionally, we hypothesized that dual-task resistance exercise would have similar effects on mood, depression, physical function, and activities of daily living (ADL) as resistance exercise.

## Methods

### Design and ethic

This study was designed as a single-blinded, randomized controlled trial. This study was approved by the CHA University Institutional Review Board on August 14, 2020 (No.1044308-202006-HR-019-02). This study was registered with the Clinical Research Information Service (WHO International Clinical Trials Registry Platform) on September 9, 2020 (study identifier, KCT0005389). Before participating in the study, participants were informed about the research procedure, and informed consent was obtained from all participants involved.

### Participants

Among those wishing to participate, those who satisfied the following conditions were selected as participants [30, 31]; (1) those who were 65 years of age or older, (2) those with The Mini-Mental State Examination-Korean (MMSE-K) score of 23 or less, (3) those who could walk without a walking aid, and (4) those who could communicate in Korean and follow the instructions of the research team. The exclusion criteria were as follows: (1) history of stroke with movement impairment, (2) history of traumatic brain injury with a movement disorder, and (3) neurological or mental comorbidity other than cognitive impairment.

### Sample size

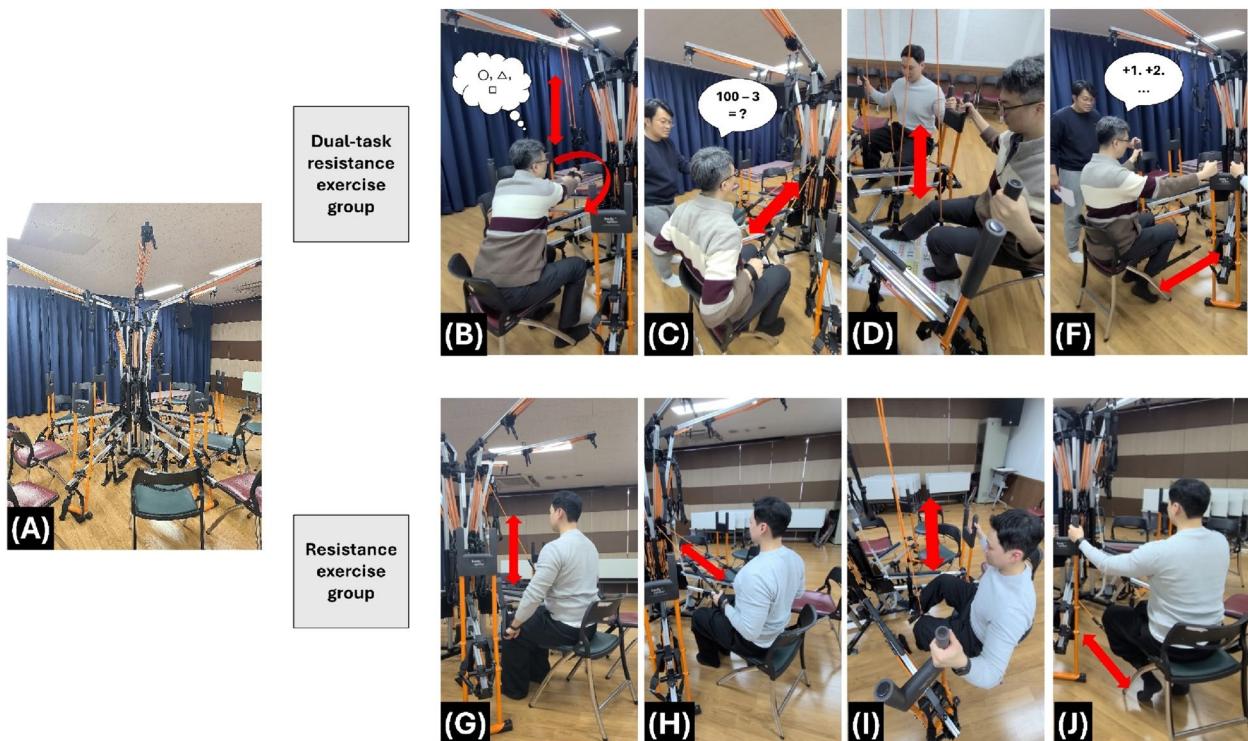
To calculate the sample size, G\*Power 3.1.9.7 (Universität Kiel, Kiel, Germany) was used, with an effect size of 0.25 (medium effect size) [32], ANOVA (repeated measures, within-between interaction), and two repeated measures. Thirty-four participants were required to achieve 80% power at an  $\alpha$  level of 0.05. Based on these values, 43 participants were required, with a 20% dropout rate.

### Intervention

Each group performed an exercise using a body spider (KOOPERA, Germany) for 40 min per session, three times a week, for 6 weeks (18 sessions) [33]. A body spider is an exercise device that uses the elasticity of a rubber rope, and both concentric and eccentric contractions are possible. It comprises a three-stage frame of the upper, middle, and lower parts; therefore, it is capable of whole-body exercise in various directions. Body spider was also used to confirm the effects of exercise in older adults [34]. The experimental group performed a dual-task resistance exercise program to improve cognitive function, and the control group performed a resistance exercise program for the same period using the same equipment (Table 1; Fig. 1). The individuals included in Fig. 1 are members of our research team, and we obtained written consent from them for publication. In both groups, warm-up exercise was performed for 10 min before main exercise and cool-down exercise was performed for 10 min after main exercise. The experimental group performed dual tasks such as writing names, drawing pictures, and subtracting numbers while performing the same resistance exercise applied to the control group. The control group performed resistance exercises for 20 min. At this time, the strength of the resistance exercise was measured at

**Table 1** Dual-task resistance exercise and resistance exercise

Categories	Dual-task resistance exercise	Resistance exercise
Warm-up exercise (10 min)	Clapping, shoulders, ankles, and toes stretching, knees pulling to chest, chair stand up.	
Main exercise (20 min)	(B) While sitting on a chair, pull the pulley from top to bottom to write names and numbers and draw shapes.  (C) While sitting on a chair, pull the pulley parallel to the ground with your arm and repeat the mental arithmetic by subtracting 3 from 100.  (D) While sitting on a chair, hook a pulley to your feet and move your feet in line with the numeric footrests installed on the floor.  (E) While sitting on a chair, hang a pulley on your ankle, bend your knees to pull the pulley parallel to the ground, and repeat mental arithmetic adding 1 to 2.	(F) While sitting on a chair, pull the pulley from top to bottom.  (G) While sitting on a chair, pull the pulley parallel to the ground with your arm.  (H) While sitting on a chair, hook a pulley to your feet and flex your hip joint.  (I) While sitting on a chair, hang a pulley on your ankle, bend your knees to pull the pulley parallel to the ground.
Cool-down exercise (10 min)	Neck, shoulder, and trunk rotation, upper and lower extremities brushing, breathing.	



**Fig. 1** Dual-task resistance exercise and resistance exercise. **A** Body Spider, **B-F** Dual-task resistance exercise, **G-J** Resistance exercise

1RM, and 3 sets were performed with approximately 10 reps per set, with a maximum of 12RM.

### Outcome measures

#### Primary variable (cognitive function)

The MMSE-K was used to investigate changes in cognitive function. The MMSE-K consists of time orientation (five points), place orientation (five points), memory registration (three points), memory recall (three points), attention and calculation ability (five points), language function (seven points), and comprehension (two points). It consists of seven sub-items of judgment ability (two points), with a total score of 30 points. When the MMSE-K score exceeds 24, it is classified as definitively normal, and when it is under 24, it is judged that the cognitive function has deteriorated. This tool has excellent validity (0.93) [35].

#### Secondary variables (Mood state, Depression state, functional fitness, activities of daily living)

The Korean version of the Profile of Mood States (K-POMS) was used to assess participants' mood states. The mood state profile has a total of 30 items and consists of six sub-domains: tension, depression, anger, vigor, fatigue, and confusion. Responses were categorized using a 5-point Likert scale with 0, 1, 2, 3, and 4 points for 'not at all,' 'a little,' 'moderately,' 'quite a lot,' and 'extremely,' respectively. The total mood disturbance is the sum of the scores of all five negative indicators (tension, depression, anger, fatigue, and confusion) among the subcategories minus the positive indicator (vigor). A higher total score for mood state is interpreted as a lower mood state for the participant. The reliability coefficient is 0.93 [36].

The Korean geriatric depression scale (GDS-K) was used to assess older adults with the symptoms of depression. This measurement method is a nutrient scale in which the participant responds with yes/no, and 18 or more out of 30 items indicate depression. The Cronbach's alpha coefficient of the GDS-K is 0.90 [37].

Functional fitness was evaluated using the Senior Fitness Test (SFT) compiled by Rikli and Jones in 1999 [38]. Among the sub-items of the senior fitness test, a hand-held dynamometer instead of the 30-sec arm curl was used to evaluate upper extremity strength, a 30-sec chair stand to evaluate the remaining lower extremity strength, a 2-min step walk to evaluate endurance, 244 cm up and go to evaluate agility, back scratch to evaluate upper extremity flexibility, and chair sit and reach to evaluate lower extremity flexibility. Additionally, a one-leg standing test was used to evaluate static balance [39]. These assessments are also useful to investigate the risk of falls in older adults [40–42].

The Korean ADL (K-ADL) scale was used to quantify the participants' ADL. The tool completed seven sub-items (dressing, washing face, bathing, eating, moving, using the toilet, and toileting) on a 3-point scale: (1) able to do alone without assistance, (2) need partial help, and (3) totally need help. It was structured to respond on a scale. The Cronbach's alpha of the K-ADL was 0.93 [43].

### Procedure

In this study, A recruitment notice was posted at a senior day care center located in Goyang, South Korea. Participants who agreed to participate and met the inclusion criteria were randomly assigned to experimental and control groups using permuted block randomization (block size 4). Allocation concealment was performed by placing sequentially numbered, opaque, and sealed envelopes. Participants were randomly allocated to an experimental group that performed a dual-task resistance exercise program for cognitive function improvement and a control group that performed a resistance exercise program. All assessments and interventions were conducted in the senior day care center.

Interventions were conducted for 40 min per session, three times a week, 18 times for 6 weeks, from October 13 to November 21, 2020 (18 sessions). All interventions were performed under the supervision of two physical therapists with 3 or more years of clinical experience. Five (or four) older adults and one physical therapist were a team. Both the experimental group and the control group were composed of 5 teams. Participants performed exercises using body spiders following the instructions of the physical therapist. Except for the chair stand up of the warm-up exercise, all exercises were performed in a sitting position. A physical therapist in each group instructed each group's exercise until all interventions were completed.

The exercise program conducted in this study was directly supervised by a physical therapist, with the duration set at a level that ensured participants with cognitive impairment did not experience undue discomfort or burden. During all interventions and assessments, researchers and safety personnel stood right next to the participants in case anything went wrong with them. Participants were informed that they were free to withdraw from the program if they felt burdened during the study period.

When assessing cognitive function, mood state, depressive state, functional fitness, and activities of daily living, group information was not provided to the assessor. Before the intervention, the participants were asked to complete the questionnaire, and participants who had difficulty reading texts were allowed to complete the questionnaire as the researcher read it. After

18 interventions, the same variables were assessed in the same way.

### Statistical analysis

All data were analyzed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). For comparison between groups on the general characteristics of participants, the chi-square test was used for categorical variables, and the independent t-test was used for continuous variables. A mixed analysis of variance was performed to analyze the time and group interaction for each dependent variable. A paired t-test was performed for the average difference between two time points in each group, and the significance level was corrected using Bonferroni correction. The statistical significance level was set at  $\alpha=0.05$ .

## Results

### General characteristics of participants

Of the 54 recruits, three declined to participate and seven met the exclusion criteria. A total of 44 people participated in the experiment, and the experiment was conducted by randomly dividing the participants into 2 groups. No person was excluded from the assessment or analysis (Fig. 2).

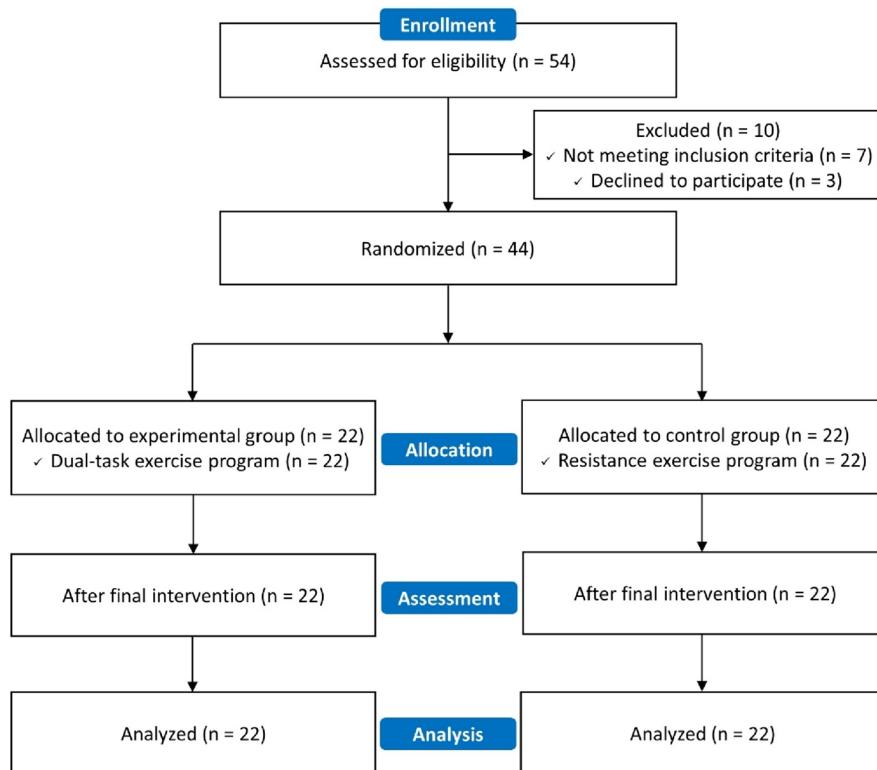
The general characteristics of the participants are presented (Table 2). Among the 44 participants, 15 (34.1%) males and 29 (65.9%) females were divided into 22 in the experimental group and 22 in the control group. Regarding sex, 7 males and 15 females were in the exercise group, and 8 males and 14 females were in the control group. There was no statistically significant difference between the experimental and control groups in sex ratio, mean age, height, weight, and body mass index. Cognitive function, mood state, depression state, functional fitness, activities of daily living showed no significant differences of pre-values between two groups.

### Cognitive function

Table 3 shows the changes in cognitive function over time between the experimental and control groups (Table 3) (Fig. 3). There was significant time and group interaction for cognitive function ( $F=4.333$ ,  $df=1$ ,  $p=0.044$ ). The cognitive scores of the experimental group significantly increased after the intervention ( $p<0.001$ ). The control group also showed a significant increase in cognitive function post-intervention ( $p<0.001$ ).

### Mood state

Table 3 shows the mood states according to time between the experimental and control groups (Table 3) (Fig. 3). There were no significant differences between the groups with respect to time ( $F=3.781$ ,  $df=1$ ,  $p=0.059$ ). The mood state scores of the experimental and control groups



**Fig. 2** Flow diagram of participants

significantly decreased after the intervention ( $p < 0.001$  for both).

#### Depression state

Table 3 shows the depression states of the experimental and control groups (Table 3) (Fig. 3). There was no significant interaction between time and group on the GDS ( $F = 2.751, df = 1, p = 0.105$ ). The depression score of the experimental group significantly decreased after the intervention ( $p < 0.001$ ), and the degree of depression in the control group showed a significant change after the intervention ( $p < 0.001$ ).

#### Functional fitness

Table 4 shows the results of significant changes in body function over time between the experimental and control groups to which the single task program was applied (Table 4) (Fig. 3). There was no significant difference between time and group in terms of physical function (back scratch,  $F < 0.001, df = 1, p = 0.986$ ; chair sit and reach,  $F = 0.001, df = 1, p = 0.977$ ; 244 cm up and go,  $F = 1.297, df = 1, p = 0.261$ ; 2-min step walk,  $F = 0.170, df = 1, p = 0.682$ ; 30-sec chair stand,  $F = 2.528, df = 1, p = 0.119$ ; left grip strength,  $F = 0.128, df = 1, p = 0.722$ ; right grip strength,  $F = 1.408, df = 1, p = 0.242$ ; one-leg

standing test  $F = 0.217, df = 1, p = 0.644$ ). In both groups, significant differences were observed before and after the intervention in all sub-variables assessed by the senior fitness test ( $p < 0.001$ ).

#### Activities of daily living

Table 4 shows the changes in ADL over time between the experimental group to which the cognitive management exercise program was applied and the control group to which the single-task exercise program was applied (Table 4) (Fig. 3). There was no significant difference between the groups with respect to time spent in ADL ( $F = 0.052, df = 1, p = 0.820$ ). The ADL score of the experimental group significantly improved after the intervention ( $p < 0.001$ ), and the ADL score of the control group significantly changed after the intervention ( $p < 0.001$ ).

#### Discussion

This study investigated the effects of dual-task resistance exercise on cognitive function, mood state, depressive state, functional fitness, and ADL in older adults with cognitive impairment. Compared to the resistance exercise group, there was a significant improvement in cognition in the dual-task resistance exercise group. Both

**Table 2** General characteristics of participants at the baseline

	Dual-task resistance exercise (n=22)	Resistance exercise (n=22)	p-value
Sex (n)			
Male	7	8	1.000
Female	15	14	
Age (year)	82.40±4.46	81.04±4.93	0.342
Height (cm)	154.94±8.13	155.30±7.34	0.877
Weight (kg)	56.82±11.96	56.87±12.09	0.990
BMI (kg/m <sup>2</sup> )	23.64±4.20	23.42±3.85	0.860
MMSE (score)	16.04±2.23	16.09±1.97	0.943
POMS (score)	72.18±3.96	72.41±3.72	0.845
GDS (score)	20.23±1.23	20.86±1.55	0.139
Senior fitness test			
Back scratch (cm)	-10.41±11.51	-5.23±9.03	0.104
Chair sit & reach (cm)	-8.86±9.76	-5.23±10.85	0.249
244 cm up & go (sec)	15.85±4.83	18.49±5.37	0.093
2-min step walk (number)	26.91±5.33	27.18±4.60	0.857
30-sec chair stand (number)	7.41±1.92	7.77±2.16	0.558
Grip strength – Lt. (kg)	15.70±7.34	17.42±7.97	0.460
Grip strength – Rt. (kg)	16.97±6.86	18.45±8.58	0.530
One leg standing (sec)	3.10±0.83	2.70±0.58	0.074
ADL (score)	13.41±1.18	13.82±1.33	0.287

Data are expressed as mean±SD or number of participants

BMI Body mass index, MMSE Mini-mental state examination, POMS Profile of mood states, GDS Geriatric depression scale, ADL Activities daily of living

**Table 3** Cognitive function, mood, and depression

	Dual-task resistance exercise			Resistance exercise			Between-group difference in change scores <sup>a</sup>	p-value (T×G)	Partial η <sup>2</sup>
	pre	post	Within-group change score <sup>a</sup>	pre	post	Within-group change score <sup>a</sup>			
MMSE (score)	16.05±2.24	18.27±2.12	2.23 (1.70, 2.76)	16.09±1.97	17.68±2.10	1.59 (1.24, 1.94)	0.64 (0.02, 1.25)	0.044*	0.094
POMS (score)	72.18±3.96	58.41±5.16	-13.77 (-16.67, -10.88)	72.41±3.73	55.36±5.21	-17.05 (-19.01, -15.08)	-3.27 (-6.67, 0.12)	0.059	0.083
GDS (score)	20.23±1.23	17.27±1.20	-2.96 (-3.65, -2.26)	20.86±1.55	18.64±1.43	-2.23 (-2.82, -1.63)	0.73 (-1.61, 0.16)	0.105	0.061

Data are expressed as mean±standard deviation or mean (95% confidence interval)<sup>a</sup>

\* Significant time and group interaction

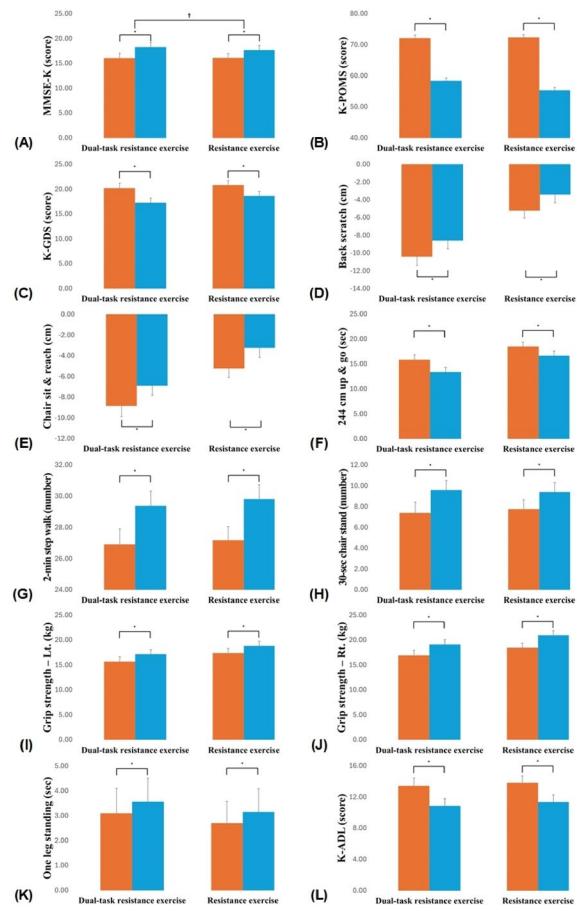
T×G, time and group interaction, MMSE Mini-mental state examination, POMS Profile of mood states, GDS Geriatric depression scale

Partial η<sup>2</sup>: effect size (small, 0.01; medium, 0.06; large, 0.14)

dual-task and resistance exercises significantly improved mood, depression, functional fitness, and ADL.

The importance of physical activity is gradually gaining attention, as previous studies have shown that an increase in physical activity improves cognitive function in older adults [44]. However, the debate continues how much more cognitive improvement benefits dual-task exercises have compared to single-task exercises [45]. The results of this study showed that performing cognitive tasks

had a significant advantage in improving cognitive function when the same amount of exercise was performed. This can be interpreted in the same context as recently published studies. In various participants, dual-tasks have been found to have advantages in cognitive function compared with single tasks [45–49]. These results suggest that secondary components, such as inhibition, planning, and execution of motor response, which activate executive functions required to respond to external



**Fig. 3** Comparisons of changes for each variable. Observed changes in each variable from pre- to post-intervention. **A** MMSE-K, **B** K-POMS, **C** K-GDS, **D** Back scratch, **E** Chair sit and reach, **F** 244 cm up and go, **G** 2-min step walk, **H** 30-sec chair stand, **I** Grip strength – Lt., **J** Grip strength – Rt., **K** One leg standing, **L** K-ADL. Orange-colored bars represent pre-intervention, while Blue-colored bars represent post-intervention. Bar length and error bar expressed mean and standard deviation, respectively. \*Significant difference in within-group; †Significant time and group interaction. MMSE-K, mini-mental state examination-KOREA; K-POMS, Korean-profile of mood states; K-GDS, Korean-geriatric depression scale; Lt., Light; Rt., Right; K-ADL, Activities daily of living

stimuli, can provide better cognitive benefits when they work together with exercise [50].

Even in the active control group that performed a resistance exercise, cognitive function showed improvement compared to that before the intervention. A previous study have also confirmed Improvements in cognition when resistance exercise was performed in older adults with reduced physical activity [51]. Improvements in cognitive function were confirmed in both groups; however, there was a significant difference in the time-group interaction between the experimental and control groups, indicating that the health

benefits of the dual-task were more effective when the intervention was performed for the same period. The human body routinely performs multiple tasks simultaneously, a concept known as dual-tasking, which is crucial for daily functioning. Older adults, especially those experiencing declines in cognitive and physical capabilities, often struggle with these simultaneous demands. Decreased cognitive and physical activity can lead to further declines in overall function [52, 53]. The results of this study showed that managing cognitive and physical functions in older adults through exercise is feasible.

Resistance exercise not only has a positive effect on cognitive function [51], reduces depression and anxiety [54, 55], and increases self-esteem and psychological well-being [56, 57]. Similar to these previous studies, both the dual-task and resistance exercise groups showed improvements in mood and depression before and after the intervention. This is not different from the results that the intensification of depression was highly correlated with cognitive functions, such as impairment of executive function and processing speed [58], and that an increase in physical activity had a positive effect on improving mood and depression in older adults [59, 60]. According to a report by Blumenthal et al., when older adults with depression were asked to exercise regularly, the depression and recurrence rates were lower in the exercise group than in the group taking antidepressant drugs for the same period [61]. Combining this with the results of this study, it is suggested that regular exercise can be as effective as drug treatment in improving depression in older adults. Additionally, physical activity, as facilitated through group exercise, such as the intervention used in this study, appears to have strengthened social networks and provided psychological stability [62–64].

Older adults who engage in regular physical activity are less likely to experience reduced mobility, perform better in ADLs and have higher levels of functional fitness [65]. Furthermore, compared to the elderly population with no physical activity at all, those engaging in physical activity have a lower risk of developing functional limitations, can maintain independence, improves quality of life, and significantly reduce the risk of death [66]. For older individuals with cognitive impairment, engaging in appropriate physical activity becomes challenging, which can make cognitive impairment more severe [67, 68]. In our study, functional fitness and ADL in both groups significantly improved after the intervention. It is presumed that participants who had low physical activity at a nursing institution experienced increased physical strength and improved efficiency in ADL by continuously practicing regular physical activity [69]. This means that social medical expenses can be reduced by preventing

**Table 4** Functional fitness and activities of daily living

	Dual-task resistance exercise			Resistance exercise			Between-group difference in change scores <sup>a</sup>	p-value (T×G)	Partial η <sup>2</sup>
	pre	post	Within-group change score <sup>a</sup>	pre	post	Within-group change score <sup>a</sup>			
<b>Senior fitness test</b>									
Back scratch (cm)	-10.41±11.51	-8.59±11.26	1.82 (1.44, 2.19)	-5.23±9.03	-3.41±8.90	1.82 (1.43, 2.21)	-0.00 (-0.53, 0.52)	0.986	<0.001
Chair sit & reach (cm)	-8.86±9.76	-6.89±9.35	1.97 (1.10, 2.84)	-5.23±10.85	-3.24±10.71	1.99 (1.58, 2.39)	-0.01 (-0.94, 0.92)	0.977	<0.001
244 cm up & go (sec)	15.85±4.83	13.40±3.71	-2.45 (-3.52, -1.38)	18.49±5.37	16.65±5.55	-1.85 (-2.12, -1.58)	0.60 (-1.68, 0.47)	0.261	0.030
2-min step Walk (number)	26.91±5.33	29.40±5.41	2.50 (1.99, 3.01)	27.18±4.61	29.82±4.66	2.64 (2.17, 3.10)	-0.14 (-0.80, 0.53)	0.682	0.004
30-sec chair stand (number)	7.41±1.92	9.59±1.74	2.18 (1.59, 2.77)	7.77±2.16	9.41±2.46	1.64 (1.24, 2.04)	0.55 (-0.15, 1.24)	0.119	0.057
Grip strength - Lt. (kg)	15.70±7.34	17.19±7.12	1.50 (0.99, 2.00)	17.42±7.97	18.81±7.88	1.39 (1.05, 1.73)	0.10 (-0.49, 0.70)	0.722	0.003
Grip strength - Rt. (kg)	16.97±6.86	19.11±7.16	2.13 (1.68, 2.58)	18.46±8.58	20.96±8.66	2.50 (2.04, 2.96)	-0.37 (-0.99, 0.26)	0.242	0.032
One leg standing (sec)	3.10±0.83	3.57±0.92	0.48 (0.35, 0.60)	2.71±0.58	3.15±0.56	0.45 (0.38, 0.52)	0.03 (-0.11, 0.17)	0.644	0.005
ADL (score)	13.41±1.18	10.86±0.94	-2.55 (-3.09, -2.00)	13.82±1.33	11.36±1.00	-2.45 (-3.08, -1.83)	0.09 (-0.71, 0.89)	0.820	0.001

Data are expressed as mean ± standard deviation or mean (95% confidence interval)<sup>a</sup>

EG Experimental group, CG Control group, T × G, time and group interaction, T Time, G Group, SFT Senior fitness test, ADL Activities daily of living

Partial  $\eta^2$ : effect size (small, 0.01; medium, 0.06; large, 0.14)

the aggravation of disabilities and diseases experienced in daily life through exercise [70].

Although the importance of physical functioning is greatly emphasized across all age groups, maintaining and improving cognitive function tends to be seen as a limited social problem in some populations [71]. However, as mentioned earlier, cognitive function is closely related to depression and has a social advantage in that it increases the quality of life of older adults by inducing the resolution of negative emotions through the improvement of cognitive function. Therefore, the maintenance and improvement of cognitive function in human health promotion is an issue that should be considered along with physical function [72].

This study presents a specific approach to exercise interventions for older adults with cognitive impairment by comparing the effects of dual-task resistance exercise against resistance training. Dual-task resistance exercise demonstrated greater effectiveness in improving cognition while producing equivalent results to resistance exercise applied at the same frequency and duration. This study contributes to the understanding of exercise science by providing a comprehensive assessment of how such interventions impact cognition,

mood, depression, physical function, and activities of daily living. The findings suggest dual-task resistance exercises may serve as a more effective method for improving cognitive and physical health in aging populations. Additionally, it contributes to the growing body of evidence supporting dual-task exercise programs as essential tools in managing cognitive health. Lastly, the study lays a foundation for future research, encouraging further exploration into optimizing exercise interventions for cognitive improvement among older adults.

This study has some limitations. First, because the participants knew the group to which they belonged, the possibility of the risk of performance bias cannot be excluded. Second, by comparing only before and after the intervention, it was not possible to determine the most appropriate intervention dose. Third, since follow-up assessments were not performed, the persistence of the intervention effect cannot be determined. Lastly, MMSE used in cognitive assessment is a tool with high reliability and validity, but individual characteristics such as education level or social background may influence the results, and that it may have limitations in detecting cognitive impairment at an early stage or certain types of cognitive impairment [73].

## Conclusion

The 6-week dual-task resistance exercise program was more effective than the resistant exercise program in improving cognitive function in older adults with cognitive impairment. Both dual-task resistance exercise and resistance exercise groups significantly improved mood, depression, functional fitness, and ADL after the intervention. For mood, depression, functional fitness, and ADL, equivalent effects were confirmed between dual-task resistance exercise and resistance exercise groups. Based on this study's results, we propose using dual-task resistance exercises for cognitive and physical health management in the older adult population.

## Abbreviations

ADL	Activities of Daily Living
GDS	Geriatric Depression Scale
MMSE	Mini-Mental State Examination
POMS	Profile Of Mood States
SFT	Senior Fitness Test

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## Authors' contributions

JEB contributed to the conceptualization, investigation, formal analysis, project administration, and writing of the original draft. SJH contributed to the conceptualization, investigation, formal analysis, data curation, and writing of the original draft. MK contributed to the resources, investigation, and funding acquisition. HWC contributed to the methodology, investigation, resources, supervision, and writing of the manuscript (review/editing). SCH contributed to the conceptualization, methodology, investigation, supervision, and writing of the manuscript (review/editing). All authors have read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

This study was approved by the CHA University Institutional Review Board (No.1044308-202006-HR-019-02). This study was registered with the Clinical Research Information Service (WHO International Clinical Trials Registry Platform) (Registration ID, KCT0005389; Registration date, 09/09/2020). Before participating in the study, participants were informed about the research procedure, and informed consent was obtained from all participants involved.

### Consent for publication

Written informed consent for publication has been obtained from the participants in this study.

### Competing interests

The authors declare no competing interests.

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Heart failure (HF) is a worldwide public health problem associated with considerable morbidity, mortality and diminished quality of life.<sup>1</sup> Although medications can improve some symptoms, individuals with HF with either preserved or reduced ejection fraction (HFpEF, HFrEF) continue to experience debilitating symptomatology, including exercise intolerance. In addition to physical symptoms, depressive symptoms are present in up to 30% of HF patients,<sup>2, 3</sup> and are associated with increased mortality, clinical events, hospitalization, and general health care use.<sup>4</sup> Yet the efficacy of antidepressant therapy in patients with coronary heart disease has been limited.<sup>5</sup> The goal of exercise interventions in this chronic disease group is primarily to improve symptoms and the quality and duration of life<sup>6</sup>. Research literature suggests vigorous exercise improves cardiorespiratory fitness<sup>7</sup>, and can produce substantial reductions in depression symptoms in patients with HF<sup>8–10</sup>. However, many exercise intervention studies consist of participants that are younger than the typical HF patient, with little comorbidity. The HF-ACTION study included participants with a median age of 59 yr (range 51–67 yr), and excluded patients with major comorbidities or limitations that could interfere with exercise training and/or with devices that limited the ability to achieve target heart rates<sup>11</sup>. Meanwhile, over 80% of HF patients are > 65 yr of age and approximately 50% are > 80 yr<sup>12</sup>. Many patients with HF have limited capacity for vigorous exercise due to comorbidities such as sarcopenia<sup>13</sup>, anemia,<sup>14</sup> obesity, diabetes, chronic obstructive lung disease (COPD), peripheral artery disease, and advanced age<sup>15, 16</sup>.

In contrast to conventional exercise, tai chi (TC) is composed of low-impact, mindfully meditative movements with integrated breathing techniques that generate a mild to moderate workout<sup>17</sup>. Many TC interventions have been studied specifically in elderly and frail cohorts and are well tolerated across fitness levels<sup>18</sup>. Research suggests that practicing TC is effective for reducing depression symptoms in a broad range of patients with HF, as compared to treatment as usual<sup>17, 19</sup>. Meanwhile, resistance exercise is effective for increasing muscle strength, endurance, physical function (six minute walk test [6MWT]), and promoting favorable arterial remodeling<sup>20</sup>. However, there are few if any studies that have examined resistance exercise for effects on depression symptoms in patients with HF.

Moreover, few studies have investigated whether TC differs from more conventional exercises for reducing depression symptoms, particularly in patients with HF. A small study ( $n = 16$ ) examined effects of TC versus aerobic exercise in patients with HF and HFpEF, finding that TC was more effective in reducing depression symptoms<sup>21</sup>.

The overall goal of this investigation was to compare TC, RB exercise, and TAU for changes in physical, cardiac, and psychological function. Associated with the primary aims of our investigation, we hypothesized that mild-to-moderate exercise practices including TC and RB would be more effective in improving physical and cardiac function compared with TAU but would not differ from each other. Associated with our secondary aim, we hypothesized that TC would be more effective than RB and TAU for reducing depressive symptoms.

## METHODS

This study was approved by the VA San Diego Healthcare System (VASDHS) and University of California at San Diego (UCSD) Institutional Review Boards, and informed

consent was obtained from all participants included in the study. All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. Patients were recruited from VASDHS and UCSD Healthcare System (between 2010 – 2015). At baseline and immediately after the 16-wk intervention, physical and cardiac function, and depression symptoms were measured. This was a randomized trial and the study coordinator determined group allocation using computer generated randomization algorithms and was responsible for all patient correspondence such as group assignment and testing appointments. Recruitment, and assessment personnel were naïve to participant group assignment. Our original study protocol compared TC with health education. However, in response to NIH grant reviewers' suggestions and discussions with the NIH granting agency the health education group was replaced with another mild exercise intervention, to examine whether TC practice went beyond conventional exercise for outcomes, including depression symptoms. We also included a treatment as usual control group in the study design as a comparator of the typical disease course, in the absence of these interventions.

## PARTICIPANTS

Inclusion criteria were diagnosis with American Heart Association/ American College of Cardiology Classification Stage C symptomatic HF (both HFpEF and HFrEF) for at least 3 mo, clinically stable (not having been hospitalized for a 3-mo period), on stable doses of neurohormonal blocking agents and diuretics for at least 3 mo, no cardiac surgeries for at least 6 mo, not in an exercise program, < 40 yr of age. Exclusion criteria included presence of a psychiatric diagnosis other than major depression including psychosis, bipolar disorder and practicing TC within the previous year.

## ASSESSMENTS

The following assessments were administered pre- and post-intervention period. Six-minute walk-test was used to assess physical functional capacity. It is a reliable and reproducible method to assess the severity of heart failure in patients, having high predictive value<sup>22</sup>. Patients were instructed to walk as far as possible within 6-min in a straight corridor. The task was performed in a 25-ft walkway, blocked off from foot-traffic. This method has been regularly used by our group for similar studies<sup>17, 23</sup>. Research assistants blinded to the participant's group assignment remained at one end of the hall recording the distance. Standardized encouragement was given at 3-min into the task, i.e. "you are doing good"; "you have 3 more minutes left". Echocardiography was performed by blinded assessors at UCSD Medical Center. All pre- and post-intervention echocardiograms were quantitatively analyzed by the same physician, who was also blinded to group allocation. Briefly, pulsed doppler spectral recordings were obtained from 4 X 4-mm sample volume placed at the tips of the mitral leaflets and in the pulmonary vein and that were adjusted to yield the maximal amplitude velocity signals. Images were digitized to obtain endocardial contours and LV cavity areas at end systole from the apical 4- and 2-chamber views. This method has been shown to be a reliable method of assessing LV function and predicting mortality in patients with HF<sup>24</sup>. Ejection fractions were derived from biplane apical (2- and 4-chamber) views with use of modified Simpson's rule algorithm<sup>25</sup>. Depression symptoms were assessed with the 21-item Beck Depression Inventory –1A (BDI), which is recommended for measurement of depression in patients with cardiovascular disease, with reliability and capacity to

discriminate between depressed and non-depressed participants with broad applicability for research and clinical practice<sup>26</sup>. Cronbach's alpha = .86 for the current study.

## GROUP INTERVENTIONS

The intervention groups were Yang-style Tai Chi Chuan-Short Form (first third), and RB training (based on the Center for Disease Control's "Move" program). RB exercise was chosen as a comparison to TC due to the psychosocial and mild-to-moderate physical exertion level similarities. Both exercises can be led by an experienced instructor, performed in a group, and provided at medical care or senior centers with minimal equipment and thus easily disseminated. Participants attended TC or RB training twice/wk for 60 min/session for 16-wk. TC and RB participants were asked to practice at home for 10-20 min/day, on non-class days. Descriptions of TC and RB class content are provided (SDC1). The TC instructor is a certified holistic health practitioner with > 10 yr of experience teaching TC to chronically ill and older adults. The RB instructor has her master's degree in nutrition and taught physical fitness for 10 yr. Both groups were asked to exercise at a perceived exertion rating of "moderate difficult", according to the Borg scale<sup>27</sup>. Classes for the 2 groups were held on different days of the week at different locations within the University to avoid cross-contamination. Written materials were provided to support home practice for both groups. All participants continued to receive usual care, including regular visits to their cardiologist, primary care physicians, and other health specialists. TAU participants did not receive an active intervention.

## STATISTICAL ANALYSES

Analyses were performed using SPSS version 24 (IBM Corp). Skewed data distribution was determined by the Kolmogorov-Smirnov test. All continuous variables approximated a normal distribution with skewness and kurtosis < 1.0. Baseline differences between groups were examined using analysis of variance for continuously measured variables and  $\chi^2$  statistics for non-continuous variables. Mixed-effects models were used to analyze the efficacy of TC compared with RB exercises and TAU over 16 wk of treatment<sup>28</sup>. The analysis for each outcome consisted of a model that included treatment, time, and treatment  $\times$  time interaction as fixed effects with a heterogeneous covariance matrix. Post hoc analyses were performed to make specific group comparisons with repeated measures ANCOVA using estimated mean imputation.

## RESULTS

Of 135 individuals screened for eligibility (see Figure 1, flow diagram) 70 patients were enrolled into the study with a median age of 66 yr (range, 45 – 89 yr) and 89% were male. BDI scores averaged  $10 \pm 7.3$  suggesting that the cohort's scores were at the cut-off for clinically significant elevation of depression symptoms ( $\geq 10$ )<sup>29</sup>. Participants were assigned to TC (n = 25), RB training (n = 22) or TAU groups (n = 23) (Table 1).

## TREATMENT FIDELITY AND ADHERENCE

Of 70 participants enrolled, 16% dropped out (TC: n = 4; RB: n = 3; TAU: n = 4) and 59 participants completed the study (n = 21, 19 and 19 respectively). There were no group

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differences in drop-out rates ( $P = .81$ ). TC participants attended a median of 87% of classes (28 sessions), and practiced a median of 74 min/wk. Whereas, the RB group attended a median of 81% of classes (26 classes) and practiced a median of 61 min/wk. There were no differences between the two active intervention groups for class attendance ( $P = .76$ ) or practice time outside of class ( $P = .86$ ). There were no differences in age, sex, %LVEF, 6MWT, HFpEF or HFrEF sub-types, BDI, scores between those who dropped out from those who completed the study ( $P$ 's  $> .10$ ). There were no serious adverse events associated with the study.

### PHYSICAL AND CARDIAC FUNCTION

Fixed effect group differences from pre- to post-intervention period were found with a mixed model analysis, with 6MWT as the dependent variable (group x time interaction,  $F = 3.19, P = .03$ ) (Figure 2). Estimated fixed effects revealed TAU significantly declined in distance walked by 205 ft [95% CI, -35 to -374,  $P = .02$ ] and the RB group with a slight increase of 70 ft [95% CI, 267 to -127,  $P = .48$ ] and TC trending for a significant decrease of 162 ft [95% CI, 21 to -345,  $P = .08$ ]. Post hoc analyses revealed only RB and TAU group differences ( $\eta^2 = .087, P = .05$ ). There were no differences between RB and TC ( $\eta^2 = .023, P = .33$ ), or between TC and TAU ( $\eta^2 = .009, P = .51$ ). Also, there were no fixed effect group differences over time in cardiac function measured with ESV ( $P = .43$ ) and %LVEF ( $P = .67$ ).

### DEPRESSION SYMPTOMS

There were fixed effect group differences over time for BDI scores (group x time interaction,  $F = 9.2, P < .01$ ) (Figure 3). Estimated fixed effects revealed a decrease in BDI scores by TC [95% CI, 2 - 5,  $P < .01$ ] and RB groups [95% CI, 1 to 5,  $P < .01$ ] of 3.5 points, while the TAU group decreased by 1 point [95% CI, -1 to 3] ( $P = .27$ ). Post hoc analyses revealed both TC ( $\eta^2 = .096, P = .039$ ) and RB ( $\eta^2 = .11, P = .034$ ) groups differed from TAU over time. There were no differences between TC and RB ( $\eta^2 = .014, P = .45$ ).

### DISCUSSION

The present investigation sought to compare TC, RB exercise, and TAU for changes in physical, cardiac, and psychological function. Over the 16-wk study, attrition was 18% which was slightly better than the 20% drop-out rate that was predicted. There were no differences in drop-out rates among the 3 groups, and no differences between intervention groups in class attendance or practice times, with median class attendance  $> 80\%$ , and reported median practice times of  $> 1$  hr/wk. There were no serious adverse events associated with the study. The median age of the participants was 66 yr, an age group representative of most HF patients.

From our primary aims, we hypothesized that mild exercise practices including TC and RB would be more effective in improving physical and cardiac function compared with TAU but would not differ from each other. However, at the end of 16 wk we failed to see improvements from baseline in physical function, measured with the 6MWT by any of the groups. Instead, we found physical function did not decline in the TC and RB group, and

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that RB and TAU differed significantly from each other over time. This may suggest that RB can hamper HF related physical function decline. Our findings illustrate that the intensity and mode of exercise used in this study does not generate the level of effect on exercise capacity that has been seen in studies with higher intensity aerobic exercise<sup>30</sup>. Our findings correspond with Yeh et al, (2011) whose study included 100 patients with HF and found no significant differences in change in 6MWT distance when comparing TC with a health education control group<sup>31</sup>. Also, our results corresponded with the literature in that RB had better outcomes on the 6MWT than TAU controls<sup>32</sup>. Of note, the RB group had a lower functional capacity (6MWT) at baseline (albeit not significantly lower) than TAU and TC, and thus the magnitude of improvement by the RB group may have been influenced by a lower baseline state.

Our hypothesis that TC and RB would improve cardiac function compared with TAU was also not supported, since there were no changes in %LVEF and ESV in any of the groups over time. This agrees with the literature suggesting that more vigorous exercise interventions have a greater likelihood of improving cardiovascular function<sup>7</sup>. Our physical and cardiac function findings should be replicated due to the small sample size, but particularly regarding physical function which may be impacted by the older age of the participants and acute and chronic HF comorbidities (e.g. claudication, COPD, diabetic neuropathy) that can impact 6MWT results.

From our secondary aim, we hypothesized that TC would be more effective than RB and TAU for reducing depressive symptoms. This hypothesis was partially supported in that TC was superior to TAU for reducing depressive symptoms over time. This is consistent with our previously published work and findings from other investigators, observing that TC practice is associated with depression symptom reductions in patients with HF<sup>17, 33</sup>. However, RB was also superior to TAU and did not differ from TC in reducing depressive symptoms. The present investigation extends prior research by including RB as a conventional exercise condition and suggests that various mild-to-moderate exercises can reduce symptoms of depression in patients with heart failure. These findings may be clinically relevant since elevated depression symptoms in cardiovascular diseases such as HF are related to greater risk of cardiovascular hospitalization and mortality<sup>34, 35, 36</sup>. More study is needed to determine the influence of exercising in groups on depression, since both interventions were group based.

A main limitation of the study includes a modest sample size resulting in limited statistical power. This precluded the inclusion of important covariates that may also influence physical and cardiac function, depression symptoms, and ultimately lessens the certainty of the findings presented. Also, because of the small sample-size we could not adequately address differences between HFrEF and HFpEF. However, both groups are known to experience reduced physical function<sup>37</sup> and depression<sup>38</sup>. Therefore, the findings relating to physical function and depression are likely relevant to both groups. Other limitations include, lack of measures for range of motion and exercise progression. Also, we had a small number of women in our study, since most patients were recruited from the Veterans hospital. Additionally, it is unclear from patient records specifically how many were taking anti-depressants.

## CONCLUSION

In sum, this study found that 2 different types of mild-to-moderate exercise training was associated with reduced depression symptoms and a potential reduction of functional decline. Importantly, patients were willing to come into a facility for group exercise when specifically recruited from cardiac clinics. Future research is needed to replicate and expand upon our findings to more fully understand the mechanisms by which mild-to-moderate exercise may reduce functional decline and depression symptoms.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments:

The protocol for the parent study can be found at [clinicaltrial.gov](#) Clinical Trial number: NCT01625819. ORCID#: 0000-0001-7633-2034

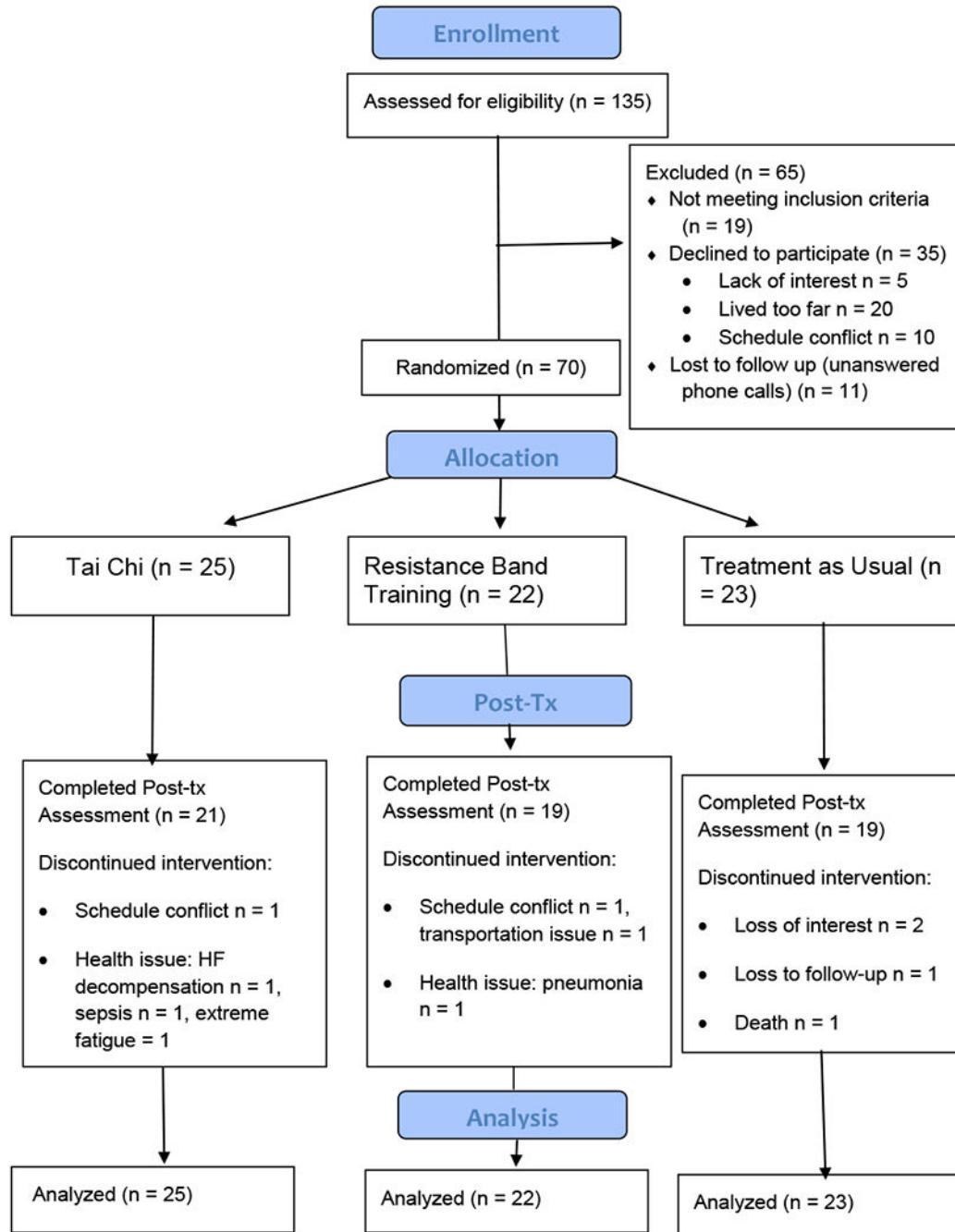
**Funding:** This research was supported by R01HL096784

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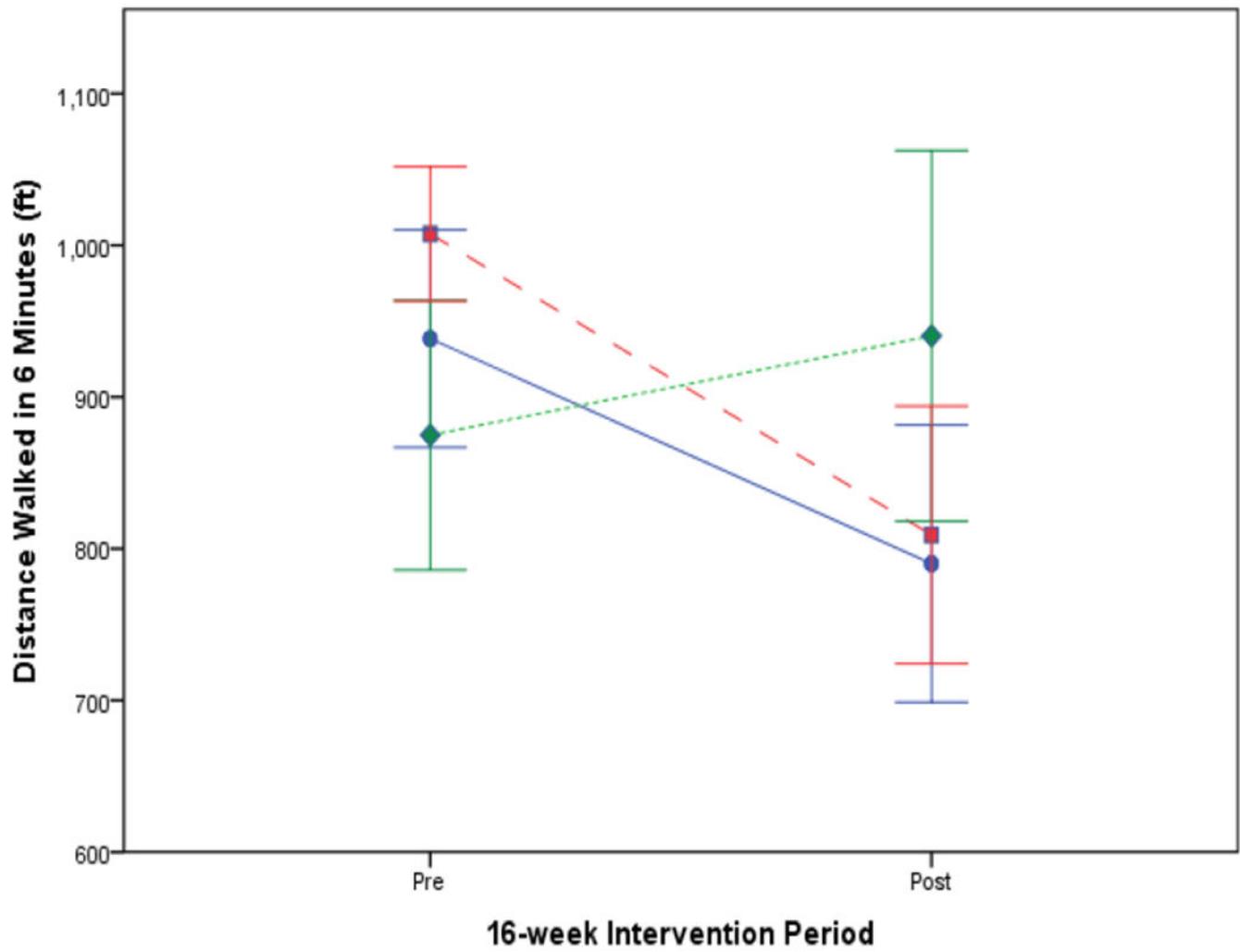
**Figure 1:**  
Participant Flow Diagram

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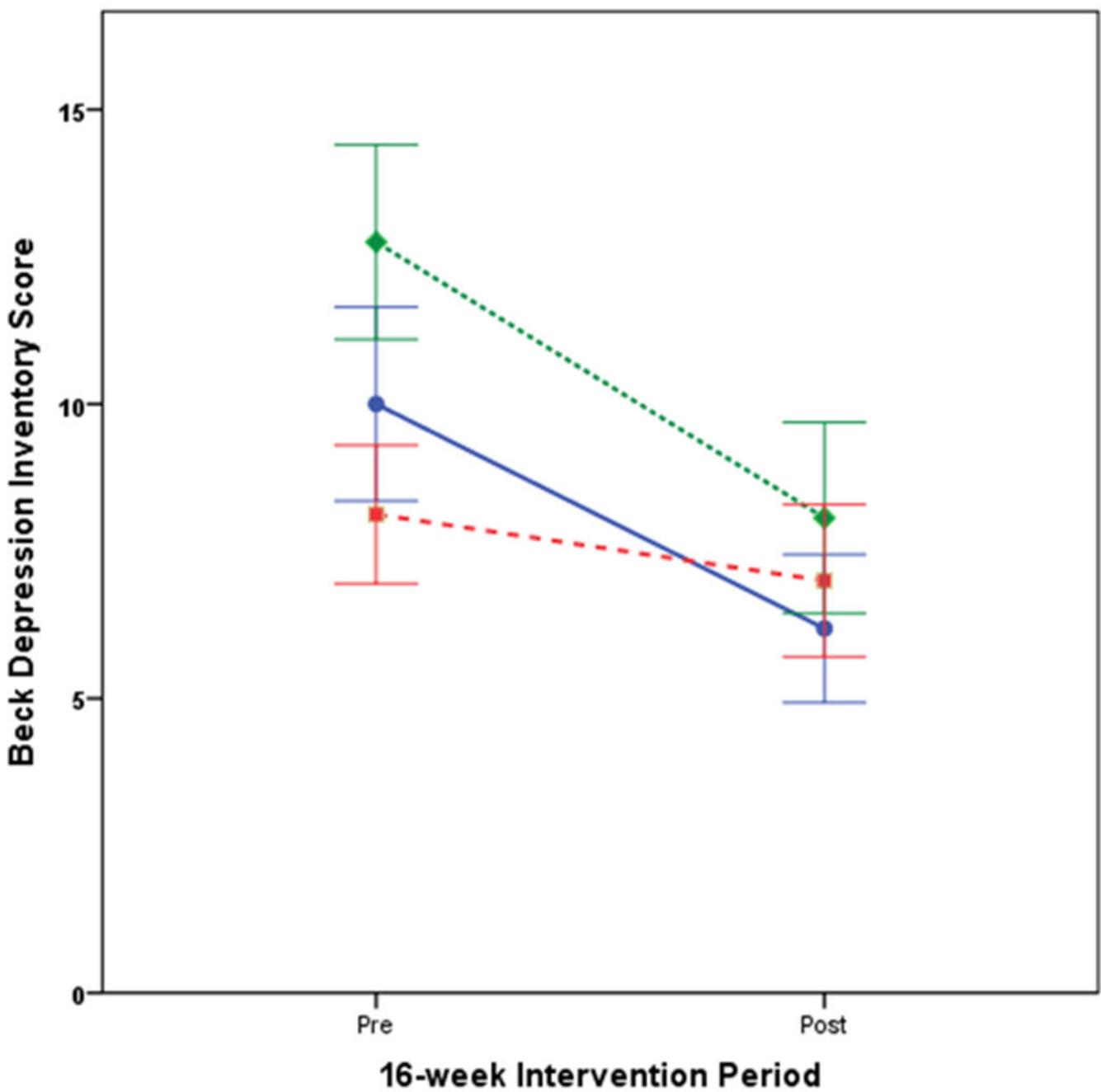
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**Figure 2.**

Changes in 6-min walk test (mean  $\pm$  SE) from baseline to post-16-wk intervention period in patients with heart failure trained in tai chi (TC) (circles), resistance bands (RB) (diamonds) exercise or treatment as usual (TAU) controls (squares).

**Figure 3.**

Changes in Beck Depression Inventory-IA scores (mean  $\pm$  SE) from baseline to post-16-wk intervention period in patients with heart failure trained in tai chi (TC; circles), resistance band (RB; diamonds) exercise or treatment as usual (TAU; squares).

**Table 1.**

## Baseline Subject Characteristics

<b>n</b>	<b>Total</b> <b>70</b>	<b>TC</b> <b>25</b>	<b>RB</b> <b>22</b>	<b>TAU</b> <b>23</b>	<b>P value</b>
Age, yr	66 ± 10	63 ± 9	65 ± 9	67 ± 7	.52
Sex, male	89	92	86	87	.81
Race, white	68	68	82	54	.29
LVEF	46 ± 14	44 ± 13	46 ± 14	46 ± 12	.85
HFrEF, n	43	44	45	37	.79
BMI, kg/m <sup>2</sup>	32 ± 8	32 ± 8	33 ± 8	31 ± 6	.64
Marital, married	30	32	23	29	.57
6MWT, ft	943 ± 336	938 ± 359	875 ± 407	1011 ± 336	.41
BDI	9 ± 7	10 ± 6	12 ± 8	8 ± 6	.17

Abbreviations: BDI = Beck Depression Index; BMI = body mass index; HFrEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; 6MWT = six-minute walk test; RB, resistance band; tai chi; TAU; TC, treatment as usual.

Data are reported as mean ± SD or n (%).

Independent t-tests and Kruskal-Wallis tests were used to evaluate group differences.

## Introduction

The benefits of physical activity (PA) are widespread through all stages of life. Specific to aging, PA prevents the natural decline of all physiological systems, decreases fall risk, maintains physical function needed for activities of daily living (ADLs), and improves quality of life (Chodzko-Zajk, 2013; Fielding et al., 2007; Manini & Pahor, 2009; Neto & Fernandes de Castro, 2012; Taylor et al., 2004). Previously, estimates of time spent in PA relied on self-report. However, many studies now use accelerometers to directly measure the amount of activity in different intensities (i.e., sedentary, light, moderate, vigorous) (Troiano, McClain, Brychta, & Chen, 2014). Accelerometer devices, particularly with older adults and in intervention trials, help mitigate inherent biases of self-report. However, advancements in the data available from accelerometers and new methods to process these data make it challenging to compare studies that apply different processing methods.

With advancements in technology, accelerometry data processing has evolved over time. Early laboratory calibration studies, primarily conducted in young to middle-aged adults, developed specific cut-points based on accelerometer counts per minute (cpm) that serve to determine the amount of time spent in moderate-to-vigorous physical activity (MVPA) (Freedson, Melanson, & Sirard, 1998; Troiano, Berrigan, Dodd, Masse, & McDowell, 2008). However, the natural decline in physical capacity with age requires an older adult to move at a higher relative intensity to accomplish tasks that take less effort by a younger individual. Thus, cut-points that were developed in younger populations often misclassify the activity levels for older adults by underestimating the amount of physical activity. This underestimation is important when applied to physical activity interventions because the data will not capture meaningful behavior changes and may appear unresponsiveness to the changes in physical activity. Thus, recent studies have developed other cut-points and equations for intensities specific to older adults from laboratory datasets (Bai et al., 2016; Copeland & Esliger, 2009; Evenson et al., 2015). It is likely, however that activities undertaken in a laboratory setting or a clinical test environment (such as the 400-meter walk (MW)) do not represent activities undertaken by individuals when they are unobserved in their natural environment. Accelerometers worn in a free-living setting for multiple days can assess habitual physical activity. Rosenberg et al. (2017) also developed and validated a machine learned algorithm from free living data to classify physical activity walking behavior in older women, a preferable form of physical activity for older adults.

Other studies have also recognized the wide variability of physical capacity in older adults and have proposed a need for a relative, or “individualized” cut-point, based on an individual’s fitness level or performance on a field measure (Miller, Strath, Swartz, & Cashin, 2010; Ozemek, Cochran, Strath, Byun, & Kaminsky, 2013; Pruitt, et al., 2008; Rejeski et al., 2016; Rejeski et al., 2017; Zisko et al., 2015). Pruitt et al., (2008) and Rejeski et al., (2016) applied an individualized cut-point based on the mean and median accelerometer cpm during a walking session, respectively. In the study by Rejeski et al., (2016), based on an individualized threshold using an equation with age, age<sup>2</sup>, and gait speed from a 400-MW, they found different levels of MVPA, compared with traditional absolute cut-points (760, 1041, and 1952 cpm) (Rejeski et al., 2016; Troiano, Berrigan, Masse, & McDowell, 2008). The tailored equation also detected statistically significant

changes in physical activity level over their 6-month physical activity intervention that were not detected with traditional cut-points. There were additional differences between traditional cut-points and the individualized equation in levels of physical activity when divided by age group.. While this study did not have a physiological comparison with the accelerometer data (e.g., heart rate or metabolic equivalent threshold data), the wide variability of physical capacity in older adults supports individualized cut-points. However, previous studies have not reported an individualized cut-point and associations to health outcomes. It is important to understand the relationship between an increased activity level and improved health outcomes, particularly for maintaining independence in older adults. Further, application to epidemiological surveillance studies is challenging without accurate information about an individual's functional capacity.

While there are now multiple new data processing methods for accelerometer data in older adults, studies have not applied these new methods to intervention data to compare the ability of each method to assess change in behavior and to relate that change to health outcomes (Bai et al., 2015; Evenson et al., 2015; Rejeski et al., 2016). The association of changes in physical activity levels with different methods and their comparison to health outcomes is crucial for activity recommendations for older adults. Thus, the purpose of the current study was two-fold:

- 1.) First, to compare five previously reported processing methods for analyzing physical activity in older adults, applied to free living accelerometer data during two time points (baseline and six months). We applied five different methods to analyze accelerometer data, including: a traditional cut-point for MVPA, a 15-second vector magnitude (VM) cut-point for MVPA, a 1-second VM algorithm, a machine learned algorithm for walking, and an individualized cut-point derived from a 400-MW, in 144 female older adults ages 67-98 years old.
- 2.) Second, to assess how the changes in physical activity with each of these different methods were associated to intervention-related changes in health outcomes of physical functioning and depressive symptoms over six months.

## Methods

### Design & Participants

This study consisted of a subsample of older adult females from a 6-month cluster-randomized controlled PA intervention in retirement communities (Kerr et al., 2012). Only females were included in the analyses because three of the methods were developed specifically for older women and have not been validated in older men. Inclusion criteria for the intervention included: a.) Age 65 years or older who could speak and read English; b) provided informed consent and completed a post-consent comprehension test; c) have no history of falls within the past year that resulted in a hospitalization; d) able to walk 20 meters without human assistance; e) complete the Timed Up & Go Test in less than 30 seconds. These criteria were established for the safety of the participants in this unsupervised walking program. All subjects gave written informed consent and approval for the study was obtained by the Institutional Review Board for the protection of human

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subjects. Health outcomes and accelerometer measures were assessed at baseline and six months. Since this study was a methodological comparison, only complete cases were included so statistical comparisons could be made. Further, we selected two outcomes to study one physical, one emotional. These were chosen as examples to compare the different accelerometer methods and is not meant to represent all possible relationships.

**Protocol.**—The details of the intervention protocol can be found in clinical trial protocol # 150336 and have been described in Kerr et al., 2012.

### Health Outcomes

**Physical Function.**—Physical function was assessed with the Short Physical Performance Battery (SPPB). The SPPB consists of three physical assessments testing balance, gait speed, and lower body strength. Each assessment is scored up to four points to calculate a total score out of 12 points; a higher score indicates better performance. Balance, gait, and lower body strength were examined by ability to stand with the feet together in the side-by-side, semi-tandem, and tandem positions; time to walk four meters at a normal pace; and time to rise from a chair and return to the seated position five times. The SPPB has shown to have evidence of validity and reliability in older adults (Gurlanik et al., 1994). Individuals with a score of ten or less have shown to have three times higher odds of walking disability within three years (Vasunilashorn et al., 2009).

**Depressive Symptoms.**—Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale Short Form (CES-D). Participants responded to ten questions (e.g., I was bothered by things that usually don't bother me) on a 0–3-point scale based on how they have felt or behaved over the past week. Summed scores 0–30 were used for analysis; higher scores indicating greater symptoms (Andresen, Malmgren, Carter, & William, 1994).

### Accelerometer Measures and Data Processing Methods

**400-Meter walk test (400MWT).**—Participants wore a triaxial accelerometer (GT3X+, ActiGraph) on their hip and were asked to walk 400 meters as quickly as they could, while remaining safe, on a standard course set up at their retirement community. The walking test was ended if the participant: completed the walk; 15 minutes elapsed; they no longer wished to continue; or if study staff felt the participant was unsafe to continue. For the current analyses, the accelerometer data from their walk were used to calculate an individualized cut-point for physical activity. To analyze accelerometer data to determine the individualized cut-points during the 400MWT, the time of day the walk occurred was recorded and used to identify accelerometer counts achieved during the test.

**Free-living physical activity.**—Physical activity during the six days after the walk test was also measured by the accelerometer. Participants were instructed to remove the device to sleep or if it would get wet (e.g., shower, swimming). Non-wear time was determined with the Choi et al. (2011) algorithm using 90 consecutive zero counts and individuals with 4 days of at least 10 hours of valid wear time were included in the analyses. The device recorded raw acceleration at 30hz and was converted to 60-second epochs, 15-second

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epochs, and 1-second raw acceleration for data processing for the various methods using ActiLife 6.0. Table 1 summarizes the method, the epoch length, and the axis used for the data processing. These five methods were chosen based on previous use in large older adult studies (1041cpm), recent development and validation in older adult women (Evenson, Activity Index, Machine Learning), and feasibility to apply without costly metabolic equipment and testing (individualized from 400MW) (Bai et al., 2016; Copeland & Esliger, 2009; Evenson et al., 2015; Rosenberg et al., 2017).

**Individualized cut-point.**—This method was based on the counts per minute (cpm) during the baseline 400MWT. The first and last minutes of the 400MWT were removed from the analyses and then median cpm was used as the individualized cut-point. The median cpm was chosen, as this was also used in Rejeski et al. (2016). This cut-point would correspond to their activity above their “fast walking pace” for 400-meters, as directed during their 400MW test.

**Evenson cut-point.**—This cut-point was developed in the laboratory study with nine lifestyle activities with older adult women from the Objective Physical Activity and Cardiovascular Health Study (OPACH). From the calibration study, the cut-point (>518 VM counts/15 sec epoch) was calculated based on the recorded Metabolic Equivalent Threshold (MET) levels of various activities using a resting MET value of 1.0 MET= 3.0mL/kg/min with 15 second epochs, vector magnitude (VM), and normal filter (Table 4 in Evenson et al., (2015)). This cut-point with the modified 1 MET value was chosen based on the lower fitness capacity of older adults and the activities performed in daily life (Kozey, Lyden, Staudenmayer, & Freedson, 2010).

**Activity Index (AI).**—The AI was developed in the same laboratory study as the Evenson cut-point. The AI uses the variance of all three axes on the device, rather than an aggregated mean. The variance allows the device to capture the magnitude and frequency of the device’s oscillation signals when a person changes from walking to running. The AI was calculated using 1-second raw files, vector magnitude, and the Activity Index R package for TM2.0 as described in Bai et al., (2016). This activity level corresponds to treadmill walking at 2.0 miles per hour, a level of MVPA for this sample of older adults (<https://github.com/javybai/ActivityIndex>).

**Traditional cut-point.**—The traditional cut-point of 1041cpm was applied using 60-second epochs and the vertical axis. This cut-point is the most commonly used absolute cut-point to assess MVPA, derived in an older adult sample (Copeland & Esliger, 2009).

**Machine learning (ML).**—The raw (unfiltered) triaxial accelerometer data was split into minute-level windows. For each window, 41 descriptive features were calculated as described in Rosenberg et al., 2017. After applying the random forest, a minute-level sequence of probabilities of each behavior label results. These probabilities were smoothed over time using a hidden Markov model (HMM). The HMM learned the probability of transitions between behaviors (i.e., it learns that it is more common to transition from sitting to standing than sitting to walking). The HMM chooses the most likely sequence of behaviors from the sequence of probabilities output by the random forest classifier. The

classifier outputs minutes in ambulatory PA (walking), light PA, standing, and sitting. (<https://github.com/kkatellis/TLBC>). The physical activity variable for comparison for this study used the ambulatory PA (walking) time. This method will capture all walking, regardless of intensity. The algorithm was developed from free living data in older women and validated in an independent sample (Rosenberg et al., 2017).

## Statistics

All analyses were performed in R 3.3.0 and significance was set at  $p < .05$ .

**Part 1. Comparing methods of physical activity.**—For each method, minutes of physical activity per day were merged by participant number for valid days and then aggregated to mean minutes per day (min/d) of activity spent above the respective physical activity value for each method at both baseline and six months. Descriptive statistics with means, standard deviations, and medians were generated for each method of physical activity analysis and for the SPPB and CES-D.

To compare the physical activity estimates for each method ( $n_j = 5$ ) to the others, we used generalized estimating equations (GEEs) with min/d of PA for each participant ( $N_i = 144$ ) at baseline and with wear time (wt) and age as covariates:

$$Y_{ij} = B_0 + B_1 \text{Method}_j + B_2 \text{WT}_i + B_3 \text{Age}_i + \varepsilon_{ij}$$

This GEE model compared average min/d of physical activity across the methods. This model uses an exchangeable working correction structure which assumes that the variance between methods is equal. Next, to assess agreement with finer granularity, we generated a confusion matrix with each minute of accelerometry to report the percent overlap of minutes of PA for each method. For methods that were processed with less than 60-second epochs (Activity Index and Evenson), minutes with 30 seconds of PA were classified as PA minutes.

Finally, to compare intervention-related changes, we fit separate mixed effects models for each method, with a random intercept ( $\alpha_{0i}$ ), to model change over time ( $X_T$ ) and conditions ( $X_C$  i.e., intervention; reference is control) with a time\*condition ( $X_C X_T$ ) interaction:

$$Y_{ij} = B_0 + B_1 X_{iC} + B_2 X_{iT} + B_3 X_{iC} X_{iT} + \alpha_{0i} + \varepsilon_{ij}$$

Plots for changes of PA at baseline and 6 months, stratified by condition, based on the models were created to show changes of PA by condition for each method.

**Part 2. Association for changes in PA to changes in SPPB and CESD over time.**—To test the associations between changes of PA and changes in outcomes for each method we specified separate linear mixed effects models for each method of PA ascertainment and each outcome variable, adjusting for multiple measurements per person. Covariates of wear time, age, and condition (intervention or control) were added to the model:

$$Y_{ij} = B_0 + B_1 X_{ij} + B_2 WT_{ij} + B_3 Age_i + B_4 Condition_i + \alpha_{0i} + \epsilon_{ij}$$

$Y_{ij}$  = Outcome (SPPB or CESD) for  $i$ th participant and  $j$ th (0 or 6months)observations

$X_{ij}$  = min/day for the selected method of PA for  $i$ th participant and  $j$ th observation

$N= 144$  (participants)

$n= 2$  (observations at 0 and 6 months)

For this model we also used an exchangeable variance structure with a random intercept and fixed slope. The specified model assumes the residuals are normally distributed as well as the random intercepts. Additionally, a fixed slope assumes the effect overtime is constant for each condition (i.e., intervention and control).

## Results

A total of 180 females had both valid accelerometer data (>4d/10hrd) at baseline and 6 months. However, 36 participants did not have 400MW accelerometer data (either unable to complete walk or did not wear accelerometer during walk) and therefore did not have an individualized cut-point for that method. Sensitivity analyses showed significant differences between those with 400MW data and those without. Thus, to ensure a comparable sample for assessing differences in methods, only 144 females (Mean<sub>age</sub> = 83.3yrs ± 6.4) with valid accelerometer data (>4d with 10hr/d) at baseline and six months and with complete data were used for the analyses. Thus, our results may only apply to women with functioning abilities to complete the 400MW. Future studies may need to replicate analyses in a larger sample of less able women. Descriptive statistics with means, standard deviations (SDs), and medians for each PA method and outcome variable at baseline and six months are presented in Table 2.

### Part 1. Comparing Methods of Physical Activity

For comparison of minutes of PA between each method at baseline generalized estimating equations (GEE), when accounting for age and wear time, showed that there was no statistical difference between minutes of PA between the Activity Index (AI) and the Evenson or Machine Learning (ML) methods ( $p > .05$ ); the ML was also similar to the 1041cpm ( $p > .05$ ) but not Evenson method ( $p < .05$ ). There was a difference in minutes of physical activity between all methods and the individualized median cut-point ( $p < .05$ ).

Table 3 shows a confusion matrix of the percentage of overlap between each method at baseline and indicates which methods were statistically different from the GEE analyses (daily minutes). There was over 60% overlap in minutes of PA between 1041cpm, Evenson, and AI methods. Additionally, 1041 cpm had the most overlap in minutes of physical activity (42%) with the individualized median method, both were the two methods that used the vertical axis. While similar to the 1041cpm and AI in the GEE analyses, the Machine Learning (ML) method had only 43% overlap of minutes of physical activity with the

1041cpm and 60% overlap with the AI. This difference shows that while similar when analyzed at the daily level (min/d in the GEE), the ML and 1041cpm are classifying different minutes within the day as PA/non-PA between methods. The most overlap for the Machine Learning was the Activity Index (60%), both of which are methods that did not use a mean of the triaxial or vertical axis acceleration.

All methods, except the individualized median method had a significant time\*condition interaction, supporting that changes in physical activity at baseline and six months differed between the intervention and control groups. Figure 1 shows the changes of PA for each method at baseline and six months, stratified by condition of intervention (n=71) and control groups (n=73), including the *p*-values for the interactions. The Individualized median method showed increases over time but no difference between the groups. The Evenson method detected more activity at baseline, as well as, larger differences between the groups, but less change over time. The 1041cpm showed the lowest levels of activity and an increase in the control group. The Activity Index and the Machine Learning showed smaller differences between the groups at baseline, and in particular the Machine Learning detected change in the intervention group over time.

## Part 2. Association Between Changes in Physical Activity to Changes in SPPB and CESD Over Time

**Physical Functioning (SPPB).**—All methods, except for the individualized median method showed a significant relationship between minutes of physical activity and SPPB with a positive parameter estimate, supporting expected, positive associations—increases in physical activity also contributed to increases in functioning. The individualized median method was the only method to report a significant but negative coefficient.

**Depressive Symptoms (CES-D).**—All methods, except for the individualized median method showed a significant relationship between CES-D and physical activity with a negative parameter estimate, supporting that increases in physical activity contributed to decreases in depressive symptoms. The changes in time spent in physical activity using the individualized median method demonstrated a non-significant association with changes in depression.

The coefficient estimates, standard errors, and p-values for both outcomes are summarized in Table 4. Estimates represent changes in SPPB score for every one-minute in physical activity for each method. Estimates were higher for the methods that reflected higher intensities. However, this reflects the change that would be perceived if each minute were achieved. Given the difference in the change estimates for each method and the difference in minutes of physical activity achieved, we multiplied the actual minutes of change in physical activity of our intervention group by the coefficients to demonstrate the actual impact on outcomes by each method (Table 5). The Activity Index, Machine Learning, and 1041cpm methods had the highest changes in health outcomes showing 0.22 increases in SPPB score and 0.28 decreases in CES-D.

## Discussion

The current study compares five different methods of analyzing accelerometer data for physical activity in older adults and reports each method's association with health outcomes of physical function and depressive symptoms in older adult women. We report differences between methods of analyzing PA at baseline and each method's changes over six months of an intervention and control group. Additionally, we found that improvements in health outcomes (i.e., physical function, depressive symptoms) were different, depending on the method of accelerometry analysis. This study reports different amounts of physical activity are needed to achieve significant improvements health of physical function and depressive symptoms. Our study demonstrates the importance of understanding different accelerometry analysis methods for PA when comparing studies, reporting objective physical activity estimates, and applying accelerometry analysis methods to detect changes in physical activity for interventions.

### Individualized Median Cut-point

The Individualized median method was different from all other methods at baseline, was extremely variable across individuals, and did not detect differences over six months between the intervention and control groups that other methods detected. We hypothesize that older adults with lower function also have a lower baseline individualized cut-point, as shown by their 400MWT. This lower crossing threshold reflects a higher amount PA throughout the week because ADLs that are done throughout their day are above this level. In contrast, the higher functioning adults completed the test with a higher intensity walk than they normally achieve in daily life activities. Thus, the less functional older adults had higher minutes within the free-living individualized method and this then had an inverse relationship with health.

Of the other studies that analyzed individual cut-points, only two have reported changes in physical activity over time (Miller et al., 2010; Ozemek, et al., 2013; Pruitt et al., 2008; Rejeski et al., 2016; Rejeski et al., 2017; Zisko et al., 2015). Rejeski et al., 2017 is the only other study to also assess changes in PA with a health outcome (i.e., major mobility disability). Rejeski et al., 2016 compared their individualized approach to traditional methods (i.e., 760, 1041, 1952cpm) and found that their individualized method was most similar to 1041cpm. Similar to our sample, the individualized method and 1041cpm had the most percent overlap in our confusion matrix (Table 3). However, different than our study, their individualized method did detect changes in their intervention but not in their control group. This difference may be attributed to the inclusion of age and walk speed in their equation. Also, for higher functioning individuals they capped their individualized threshold at 1952cpm which would allow these participants to have more minutes of PA throughout their week than our sample who may engage in PA over 1952cpm but did not reach their individualized median cpm as often that they established during their 400MW.

Rejeski et al., 2017 examined changes in PA minutes overtime and risk for major mobility disability. They also did not see an intervention effect for the lowest functioning individuals. Similarly, while we did not split the current sample by functioning level, the individualized method was the only method that did not relate to expected increases in physical function or

depressive symptoms with increases in PA by this method. This seemingly contradictory result is likely not due to their unresponsiveness to the intervention. Rather, that low functioning individuals at baseline had a low PA threshold, yielding a high amount of minutes at baseline. Then, as they improve their functioning over the intervention, the low cut-point masks meaningful activity that is above that threshold that contribute to improved health outcomes. Thus, in follow-up measurements they have improved their functioning, yet application of their lower activity threshold does not reflect their increase in PA that contribute to their function.

### Evenson Cut-point

In our sample, the Evenson cut-point show similar PA minutes per day to the Activity Index. However, there was more minute-level overlap with the 1041cpm method, as shown in the confusion matrix, reporting 69% of the same minutes from both methods were categorized as PA. Aside from the individualized median method, this method had the highest number of total minutes, resulting in the most overlap with the individualized cut-point. However, different than the individualized cut-point, it was still sensitive to change between the intervention and control groups and was associated with both SPPB and CES-D. The intervention group increased 6.5 min/day while the control group did not increase at all. The difference between intervention and control was large at baseline. Other methods did not indicate such a difference, which would have implications for determining the effectiveness of the randomization. Although this method had the lowest changes in SPPB score, it was comparable for the CES-D outcome. Similar to the individualized cut-point it may be because of the high number of minutes accumulated that each minute is less “meaningful” towards improving functioning.

This method was also developed and validated in older adult women (Evenson et al., 2015). Lacroix et al., (2017) compared this method to a traditional cut-point (1952cpm) revealing the traditional cut-point would significantly underestimate PA in their older adult sample (Lacroix et al., 2017). While this method has not been reported by another PA intervention, Buchner et al., (2017) found that those with a low or moderate SPPB (<9) in the lowest quartile of PA (<25.1min/d) were associated with higher fall risk, than those with higher PA and that those below the median PA (<44min/d) were significantly more likely to report an injurious fall (Buchner et al., 2017). Therefore, this may be an appropriate method to detect a reduction in fall risk.

### Activity Index (AI)

Similar to the Evenson, the Activity Index was developed in the same sample of older women but had not been applied to intervention data (Bai et al., 2016). It was the only method in our sample with similar baseline PA estimates to the ML method at baseline. This similarity may reflect that both the AI and ML used different metrics than a mean count of the vertical axis or vector magnitude in the device. The AI also detected changes between intervention and control groups, showing about an 8 minutes/day increase in the intervention and no changes in the control. The AI showed the highest improvements in SPPB for minutes of PA. This finding may be because this method uses the variance of the three axes in the accelerometer which are more sensitive to changes in acceleration (e.g., moving from

walking to jogging) that are not detected by a mean value. Thus, more variability in acceleration and movement in older adults may be beneficial to physical function and meaningful to capture through accelerometer behavioral measurement. Although the AI has not yet been used frequently by other studies, Bai et al., (2016) reports several advantages in the simplicity of the algorithm. When applied to our sample, this method reveals promising advantages for detecting changes in PA as well as associations with health outcomes.

### **Traditional Cut-point (1041cpm)**

The 1041cpm method was similar to the AI and ML at baseline in minutes per day and had more minutes of overlap than any other method with the individualized method. This similarity may be due to both methods using the vertical axis only. It also was sensitive to changes between the intervention and control groups overtime. While recent studies that have reported vector magnitude to be preferable over vertical axis, our results support this method is valuable for studies that have only used uniaxial devices. Further, it is important to show that this simple method that is the most prevalent in previous literature of all of our reported methods still reflects similar outcomes to the more complex proposed methods in both minutes of PA and relationship to health outcomes overtime.

### **Machine Learning (ML)**

Although the ML method estimated similar total physical activity minutes per day with the AI and 1041cpm, when assessing each minute classified as physical activity, the ML showed much smaller overlap with each of these methods than the other methods to each other. That is, this difference demonstrates that the ML method is detecting minutes of physical activity that are different than other methods. This difference may be because it assesses a behavior, walking, regardless of the intensity. While this method specifically captures walking behavior, and minutes of PA below a level of intensity of other methods, we did not see an inflation in meaningless minutes per day as we did with the individualized threshold. Rather, this method detected the greatest increase in the intervention group over time, about 15 minutes, nearly twice as much as all other methods, aside from the individualized median cut-point. The ML method was also the only method to report decreases in the control group, which are expected in this older age group. While ML showed smaller changes in SPPB than the AI and 1041cpm for each minute of physical activity (Table 4), it was comparable to both methods when applied to the actual changes in physical activity minutes of the intervention group (Table 5). Walking is the most preferred form of PA for older adults and our intervention demonstrated older adults increased levels of walking PA that were meaningful to also improve their health. This method may be important to include in future interventions in conjunction with another method as it measures a specific behavior that captures meaningful activity that is not picked up by other methods.

### **Limitations & Future Research**

Some key characteristics of our sample may limit the generalizability to other older adult samples. First, we were only able to test the methods on women because the algorithms were developed in older women. Future studies may want to apply these methods, when validated, to older adult men, as their functioning and activity levels have shown to be different than older adult women (Marques et al., 2014). Additionally, we used only participants who

completed a 400MWT at both time points, excluding those who were not able to complete this assessment or who did not return at six months, thus our sample represents more healthy and compliant participants. Our sample also had a baseline CES-D mean score of 5.6 points, reflecting a generally emotionally healthy group. Thus, this outcome may have experienced ceiling effects and future studies may want to look at changes in depression scores with a more “depressed” population at baseline. Other studies have reported differences in physical activity with accelerometry between gait speeds and functioning levels in older adults (Corbett, Valiani, Knaggs, & Manini, 2016; Kherikahan et al., 2016; Rejeski et al., 2017). Future research also may continue to find differences in the application of the individualized median method to sub groups of older adults.

## Conclusions

Our study demonstrates a comparison of five different methods of analyzing physical activity for older adults and their relationship to health outcomes over time. Though it is not yet known what is the “best” method, researchers should be aware of these differences when designing and evaluating interventions, comparing studies, and applying to older adult populations. Future research may want to apply several of these methods together and continue to find the most appropriate method to apply for specific older adult subpopulations.

## Acknowledgments

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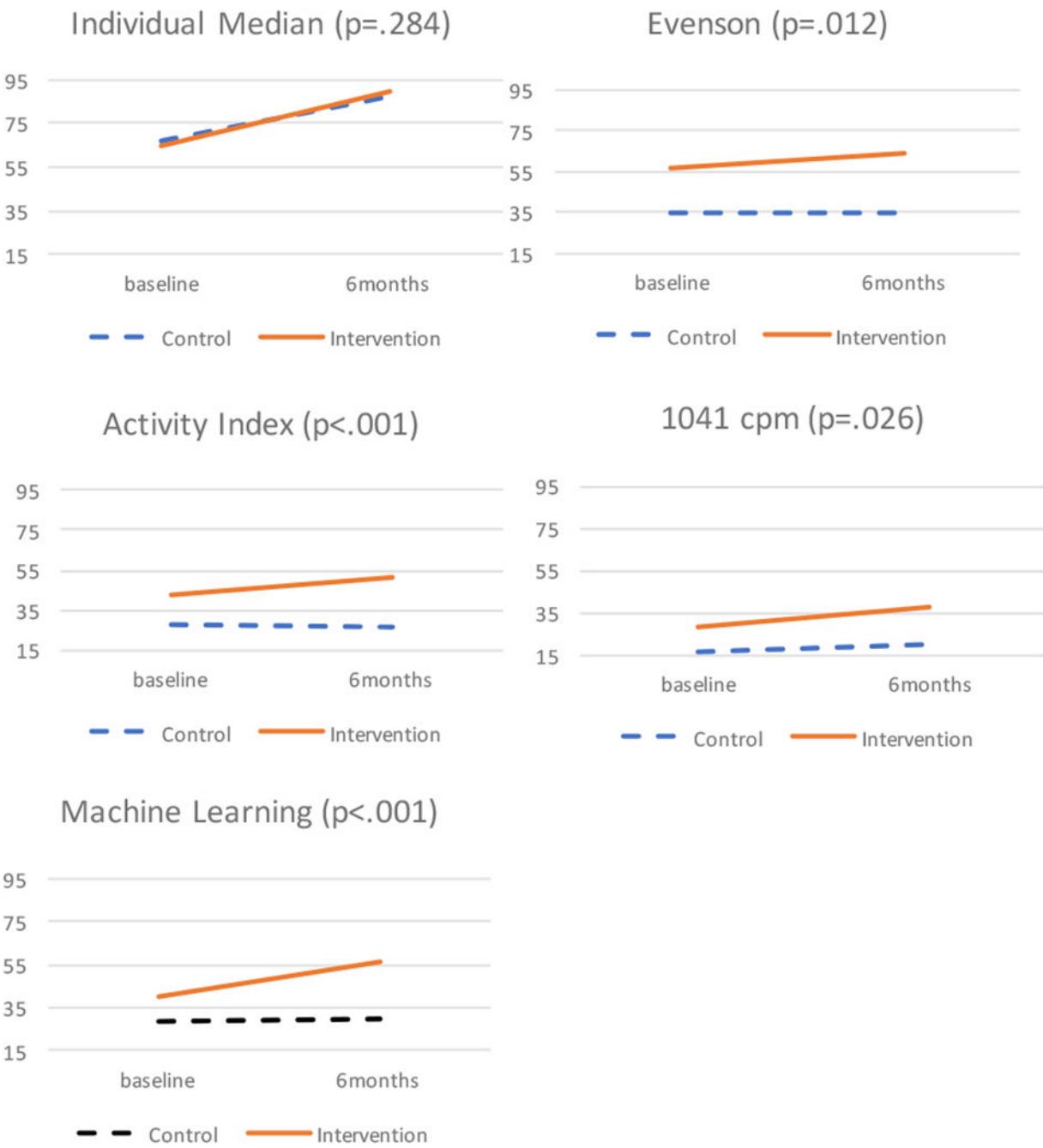
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**Figure 1.**

Minutes/day of physical activity at baseline and 6 months by condition. P value reports the Time X Condition interaction.

**Table 1**

Method, Epoch Length, and Axis Used for Accelerometry Data Processing

Method	Epochs	Axis
Individualized 400MW (>Median cpm)	60 sec	VA
Evenson	15 sec	VM
Activity Index	1 sec	VM
1041 cpm	60 sec	VA
Machine Learning	30 Hz features aggregated to 60 sec	VM

*Note.* VM: vector magnitude; VA: vertical axis; cpm: counts per minute, Hz: hertz

**Table 2**

Means, Standard Deviations (SD), and Medians for Physical Activity (min/d) and Outcome Variables for complete sample (N=144)

Method	Baseline						6 Month			
	Mean	SD	Median	LQR	HQR	Mean	SD	Median	LQR	HQR
In.Median	65.9	70.4	44.6	21.0	76.3	87.7	77.3	63.3	35.5	112.5
Evenson	45.1	27.8	41.0	23.7	59.6	49.3	34.8	41.0	23.6	66.5
AI	35.1	23.3	32.4	17.9	45.8	38.9	29.3	32.6	17.2	52.4
1041cpm	22.4	20.3	16.7	8.5	30.3	28.8	23.8	20.9	12.1	41.3
Machine Learning	35.0	23.5	29.3	19.3	47.6	43.0	33.0	36.4	19.4	58.3
<u>Health Outcomes</u>										
SPPB	8.7	2.7	9.0	7.0	11.0	8.6	2.8	9.0	9.0	7.0
CES-D	5.6	4.0	5.0	2.0	8.0	5.6	3.9	5.0	5.0	3.0

Note. In.Median: Individualized 400MW median cut-point; AI: Activity Index; SPPB: 0-12 points (sum of 3 tests; 4 points each); CES-D: 0-30 points (sum of 10 questions; 3 points each); LQR: Lower Quartile Range; HQR: Higher Quartile Range

**Table 3**

Confusion Matrix at Baseline for Each Method with Percent (%) Overlap between Methods for Each Minute of PA and Similarities (\*) between Methods for Minutes/day

	<b>In. Median</b>	<b>Evenson</b>	<b>AI</b>	<b>1041cpm</b>	<b>ML</b>
In. Median	100%	31% *	25% *	42% *	17% *
Evenson		100%	61%	69% *	42% *
AI			100%	63%	60%
1041cpm				100%	43%
ML					100%

Note.

\* indicate significant differences based on total minutes/day by GEE ( $p<.05$ );

In. Median: Individualized 400MW median cut-point; AI: Activity Index; ML: Machine Learning

**Table 4**

Each Method Entered Separately in a Regression Model Adjusting for Wear time, Age, and Condition

	<b>SPPB</b>			<b>CESD</b>		
	Estimate	SE	p value	Estimate	SE	p value
In. Median	-0.009	0.002	0.000	0.003	0.004	0.413
Evenson	0.011	0.005	0.031	-0.031	0.009	0.001
AI	0.033	0.006	0.000	-0.035	0.011	0.002
1041 cpm	0.024	0.007	0.000	-0.037	0.012	0.003
ML	0.014	0.004	0.001	-0.017	0.008	0.039

*Note.* Models included covariates of age, weartime, and condition. Estimates represent changes in SPPB or CES-D score for every 1-minute change in PA.

**Table 5**

Changes in SPPB and CESD Score by the Mean Change in PA of the Intervention Group

Method	*PA (min/d)	SPPB	CESD
In. Median	24.03	-0.22	0.07
Evenson	6.48	0.09	-0.26
AI	7.49	0.28	-0.30
1041cpm	8.05	0.22	-0.33
Machine Learning	14.83	0.24	-0.28

Note. NS: Not Significant

\* PA represents the mean change in minutes of PA (min/d) between baseline and 6 months for the intervention group

Several issues remain to be addressed. First, most previous studies have investigated the relationship using cross-sectional data, which are subject to reverse causation (ie, reciprocal relationship between depression and unhealthy lifestyle). Only two cohort studies were conducted on this topic, one in France<sup>17</sup> and the other in Australia.<sup>18</sup> Second, only one cross-sectional study investigated the association between overall lifestyle and depressive symptoms in an Asian population.<sup>23</sup> In Japan, the number of people who suffer from depression has been increasing, and its suicide rate is among the highest in the world.<sup>24</sup> Therefore, it is important to investigate the association in this particular population. Third, evidence on this subject is scarce in working populations; depression is the leading cause of sick-leave among working populations in Japan<sup>25</sup> and other developed countries.<sup>26,27</sup>

To address these issues, we aimed to examine the prospective association of the HLI, which is composed of seven modifiable lifestyle factors (including body mass index [BMI], leisure-time physical activity, smoking, alcohol intake, vegetable intake, fruit intake, and sleep duration), with depressive symptoms in a Japanese working population.

## METHODS

### Study procedure

Data for the present study were derived from the Furukawa Nutrition and Health Study, an ongoing nutritional epidemiological study conducted among workers of a manufacturing company and its affiliated companies in Japan. The details of the study have been described elsewhere.<sup>28,29</sup> The baseline survey was conducted in April 2012 (workplace A in Chiba Prefecture) or May 2013 (workplace B in Kanagawa Prefecture) through periodic health examinations. Then, the follow-up survey was conducted 3 years later. All employees ( $N = 2,828$ ) were asked to fill out two types of survey questionnaires (one for health-related lifestyle and the other for diet). We also obtained health examination data containing anthropometric and biochemical data and information on medical history. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan. Prior to the surveys, written informed consent was obtained from all of the participants.

### Participants

Of the 2,828 employees eligible for the baseline survey, 2,162 agreed to participate in the baseline survey (response rate: 76%). Of them, 2,151 participants completed the two types of questionnaires. We then excluded 610 participants with baseline depressive symptoms (defined as the Center for Epidemiologic Studies Depression Scale [CES-D] score  $\geq 16$ ), 1 participant with missing data on CES-D score, and 58 participants with a history of the following diseases at baseline (some participants had two or more diseases): cancer ( $n = 15$ ), cardiovascular disease ( $n = 17$ ), chronic hepatitis ( $n = 2$ ), kidney disease including nephritis ( $n = 8$ ), pancreatitis ( $n = 2$ ), and mental disorder, such as depression and anxiety ( $n = 18$ ). We excluded those with such diseases to preclude reverse causality due to their potential influence on lifestyles. We also excluded those with missing data for one of the exposure factors ( $n = 15$ ) and selected covariates ( $n = 26$ ) (described below) at baseline. Of the 1,441 participants above, 920 (64%) responded to the follow-up survey. Finally, we excluded three participants with missing data on CES-D score at the follow-up survey. These exclusions resulted in a total of

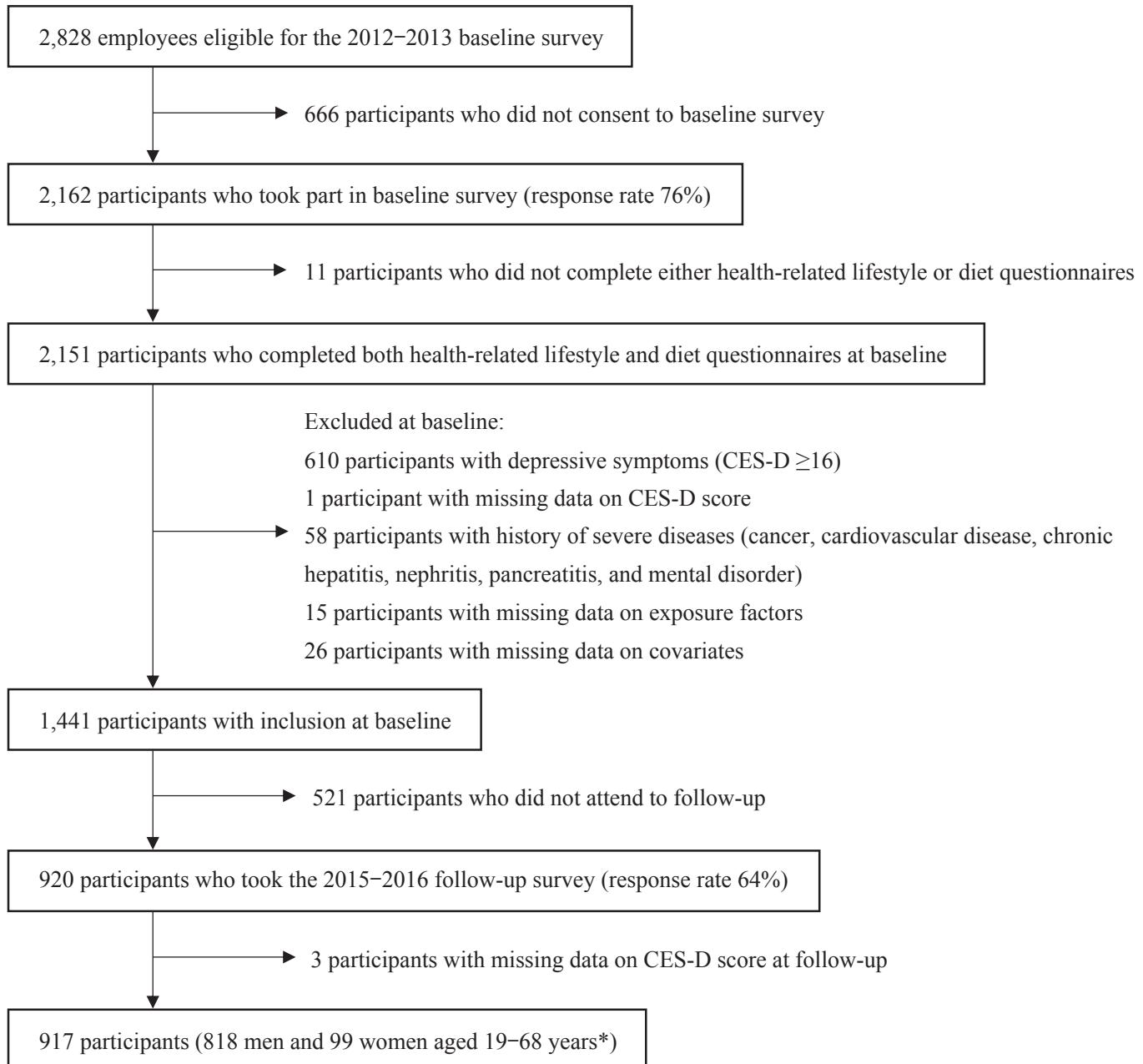
917 participants (818 men and 99 women aged 19 to 68 years) for the subsequent analysis (Figure 1).

### Construction of healthy lifestyle index

The components of the HLI included BMI, leisure-time physical activity, smoking, alcohol intake, vegetable intake, fruit intake, and sleep duration. Based on previous knowledge and international and national recommendations, each lifestyle factor was classified into two groups: low-risk (adhering to the healthy lifestyle) or high-risk (not adhering to the healthy lifestyle) group (Table 1).

Body height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, in a standardized procedure, with participants wearing light clothes and without shoes. BMI was calculated by dividing weight (kg) by the square of height ( $m^2$ ). We defined low-risk group as individuals with normal BMI (18.5–24.9 kg/m<sup>2</sup>) and high-risk group as underweight (<18.5 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>), or obese ( $\geq 30$  kg/m<sup>2</sup>) individuals.<sup>30</sup> For leisure-time physical activity, participants were asked to report frequency and duration of each light-, moderate-, and vigorous-intensity physical activities. Leisure-time physical activity was then expressed as the sum of metabolic equivalent (MET) multiplied by the duration of time engaged across activities with different intensity. Based on current physical activity recommendation,<sup>31</sup> we defined low-risk group as individuals who engaged in  $\geq 7.5$  MET-hours per week (equivalent to  $\geq 150$  minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity per week)<sup>32</sup> and high-risk group as those engaged in <7.5 MET-hours per week. With regard to smoking, we defined low-risk group as non-smokers, including never or former smokers, and high-risk group as current smokers.<sup>33</sup> The national health promotion campaign called Health Japan 21, which was established by the Ministry of Health<sup>34</sup> defines 1 *go* (a Japanese traditional unit; 180 mL) of Japanese sake (approximately 23 g ethanol) per day as moderate alcohol intake. Based on this guideline, we defined low-risk group as non-drinkers and individuals with alcohol intake of  $\leq 23$  g ethanol/day and high-risk group as those with alcohol intake of  $>23$  g ethanol/day. Vegetable and fruit intake during the preceding 1-month period was assessed via a validated brief self-administered diet history questionnaire (BDHQ), which includes 58 food and beverage items.<sup>35</sup> Based on Health Japan 21, we defined low-risk group as individuals with vegetable intake of  $\geq 350$  g/day and high-risk group as those with vegetable intake of  $<350$  g/day. For fruit intake, we referred to fruit intake recommendation by the Japanese Food Guide Spinning Top established by the Ministry of Health and Ministry of Agriculture.<sup>36</sup> We defined low-risk group as individuals with fruit intake of  $\geq 200$  g/day and high-risk group as those with fruit intake of  $<200$  g/day. As for sleep duration, given that a meta-analysis of seven prospective studies documented a significant association between short and long sleep duration and depression,<sup>14</sup> we defined low-risk group as individuals with sleep duration of 6–8.9 hours/day and high-risk group as those with short (<6 hours/day) or long ( $\geq 9$  hours/day) sleep duration.

Low- and high-risk groups received a score of 1 and 0, respectively. Summing the binary score of each seven components, the HLI score ranged from 0 to 7, with a higher score indicating a healthier lifestyle. Following the lead of Gaye et al,<sup>37</sup> who also developed a 7-item health score, we categorized the HLI into three groups: 0–2 (low), 3–4 (middle), and 5–7 (high).



CES-D, Center for Epidemiologic Studies Depression scale.

\* age at baseline

**Figure 1.** Flow chart of participant selection

### Assessment of depressive symptoms

Depressive symptoms were assessed using a Japanese version<sup>38</sup> of the CES-D scale.<sup>39</sup> The scale consists of 20 items that address six major symptoms of depression, including depressed mood, guilt or worthlessness, helplessness, or hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance experienced during the preceding week. Each item is scored on a scale of 0–3 according to the frequency of the symptom, and the scores are summed, contributing to the total CES-D score ranging from 0–60. Participants with CES-D score  $\geq 16$  are considered to have depressive symptoms.<sup>39</sup>

### Covariates

We also collected baseline information on covariates, which include age (years, continuous), sex (men or women), workplace (A or B), and marital status (married or not), employment status (permanent employee, contract employee, or part-time employee), job grade (low: general-duties grade; middle: middle management; or high: director or senior management), night or rotating shift work (yes or no), overtime work (<10, 10–29.9, or  $\geq 30$  hours/month), job strain (quartile), and CES-D score (continuous). Except for age, sex, and workplace, all covariates were ascertained via the health-related lifestyle questionnaire.

**Table 1.** Components of the Healthy Lifestyle Index

Lifestyle components	Low-risk group (score 1)	High-risk group (score 0)
Body mass index	Normal (18.5–24.9 kg/m <sup>2</sup> )	Underweight (<18.5 kg/m <sup>2</sup> ), overweight (25–29.9 kg/m <sup>2</sup> ), or obese (≥30 kg/m <sup>2</sup> )
Leisure-time physical activity	≥7.5 MET-hours/week	<7.5 MET-hours/week
Smoking status	Non-smoker (never or former)	Current smoker
Alcohol intake	≤23 g ethanol/day	>23 g ethanol/day
Vegetable intake	≥350 g/day	<350 g/day
Fruit intake	≥200 g/day	<200 g/day
Sleep duration	6–8.9 hours/day	<6 hours/day or ≥9 hours/day

MET, metabolic equivalent.

**Table 2.** Baseline characteristics of participants in the Furukawa and Nutrition Study (2012–2013) according to the Healthy Lifestyle Index categories

	Healthy Lifestyle Index		
	0–2 (low) (n = 203)	3–4 (middle) (n = 526)	5–7 (high) (n = 188)
Age, mean [SD]	42.5 [8.6]	41.9 [9.5]	41.1 [9.7]
Sex, men, n (%)	193 (95.1)	456 (86.7)	169 (89.9)
Workplace, place A, n (%)	108 (53.2)	306 (58.2)	112 (59.6)
Marital status, married, n (%)	136 (67.0)	374 (71.1)	136 (72.3)
Employment status, permanent employee, n (%)	196 (96.6)	491 (93.4)	179 (95.2)
Job grade, low, n (%)	141 (69.5)	356 (67.7)	137 (72.9)
Night or rotating shift work, yes, n (%)	58 (28.6)	89 (16.9)	19 (10.1)
Overtime work, ≥30 hours/month, n (%)	45 (22.2)	122 (23.2)	54 (28.7)
Job strain, mean [SD]	0.485 [0.124]	0.465 [0.107]	0.460 [0.103]
CES-D score at baseline, mean [SD]	9.7 [3.8]	8.2 [3.9]	7.8 [4.1]
<b>Healthy lifestyle index components</b>			
Body mass index, normal, n (%)	79 (38.9)	410 (78.0)	170 (90.4)
Smoking status, never or former, n (%)	69 (34.0)	408 (77.6)	180 (95.7)
Leisure-time physical activity, ≥7.5 MET-hours/week, n (%)	20 (9.9)	166 (31.6)	144 (76.6)
Alcohol intake, ≤23 g ethanol/day, n (%)	95 (46.8)	405 (77.0)	171 (91.0)
Vegetable intake, ≥350 g/day, n (%)	6 (3.0)	56 (10.7)	77 (41.0)
Fruit intake, ≥200 g/day, n (%)	11 (5.4)	55 (10.5)	96 (51.1)
Sleep duration, 6–8.9 hours/day, n (%)	73 (36.0)	351 (66.7)	164 (87.2)

CES-D, Center for Epidemiologic Studies Depression scale; MET, metabolic equivalent; SD, standard deviation.

## Statistical analysis

We determined frequencies and means of baseline characteristics according to the three categories of the HLI. We performed a multiple logistic regression analysis and calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of depressive symptoms. We adjusted for age, sex, and workplace in model 1. In model 2, we additionally adjusted for marital status, employment status, job grade, night or rotating shift work, overtime work, and job strain. In addition, CES-D score at baseline was further adjusted in model 3. To estimate the impact of each lifestyle component on the association between the HLI and depressive symptoms, we followed the lead of Adjibade et al<sup>17</sup> and created seven alternative versions of the HLI in which we omitted one component from the original HLI and adjusted further for the omitted component. This approach enabled us to examine the effect of the omitted component while assuming synergistic effects among the remaining six components. Statistical significance was set as *P*-trend <0.05 (two-tailed). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

Participants' baseline characteristics across the HLI categories are presented in Table 2. Compared with employees in the lowest HLI group, those in the higher HLI groups tended to be younger and married, have less night or rotating shift work, have more overtime work, lower job strain, and lower CES-D score at baseline.

We identified a total of 155 incident cases (17.0%) of depressive symptoms (CES-D ≥16) at the follow-up survey. More specifically, there were 49 (24.1%), 83 (15.8%), and 23 (12.2%) incident cases in the low, middle, and high HLI groups, respectively. Table 3 shows the results of a logistic regression analysis investigating the association between the HLI and incidence of depressive symptoms. A significant association was observed between the higher HLI at baseline and a decreased risk of depressive symptoms at the follow-up survey; ORs of depressive symptoms were 0.61 (95% CI, 0.41–0.91) for the middle and 0.44 (95% CI, 0.26–0.76) for the high HLI group, respectively (*P*-trend = 0.002). Results were similar after additional adjustment for other covariates, except for the baseline

**Table 3.** Odds ratios and 95% confidence intervals of depressive symptoms according to the Healthy Lifestyle Index categories

	Healthy Lifestyle Index			P-trend*
	0–2 (low) (n = 203)	3–4 (middle) (n = 526)	5–7 (high) (n = 188)	
Number of cases (%)	49 (24.1)	83 (15.8)	23 (12.2)	
Model 1 <sup>a</sup>	1.00 (reference)	0.61 (0.41–0.91)	0.44 (0.26–0.76)	0.002
Model 2 <sup>b</sup>	1.00 (reference)	0.62 (0.41–0.94)	0.44 (0.25–0.77)	0.003
Model 3 <sup>c</sup>	1.00 (reference)	0.74 (0.48–1.15)	0.55 (0.31–0.99)	0.041

\*Based on multiple logistic regression analysis incorporating the Healthy Lifestyle Index as a continuous variable.

<sup>a</sup>Adjusted for age (years, continuous), sex (men or women), and workplace (A or B).

<sup>b</sup>Adjusted for variables in model 1, and marital status (married or not), employment status (permanent employee, contract employee, or part-time employee), job grade (low, middle, or high), night or rotating shift work (yes or no), overtime work (<10, 10–29.9, or ≥30 hours/month), and job strain (quartile).

<sup>c</sup>Adjusted for variables in model 2 and CES-D score (continuous) at baseline.

CES-D score (model 2). After further adjustment for the baseline CES-D score (model 3), ORs of depressive symptoms were 0.74 (95% CI, 0.48–1.15) for the middle and 0.55 (95% CI, 0.31–0.99) for the high HLI group, respectively (*P*-trend = 0.041).

Analyses in which we examined the impact of each component on the association revealed that ORs of depressive symptoms for the high HLI group were attenuated when we employed the HLI without BMI (OR 0.85; 95% CI, 0.37–1.97), smoking status (OR 0.66; 95% CI, 0.27–1.60), leisure-time physical activity (OR 0.71; 95% CI, 0.34–1.49), alcohol intake (OR 0.96; 95% CI, 0.43–2.14), or sleep duration (OR 1.04; 95% CI, 0.49–2.20) (Table 4). A larger attenuation (increase of OR for the highest HLI group) was observed when sleep duration (0.49 points), alcohol intake (0.41 points), BMI (0.30 points), leisure-time physical activity (0.16 points), or smoking status (0.11 points) were omitted from the original HLI.

## DISCUSSION

In this prospective study among a Japanese working population, we found that adherence to multiple healthy lifestyles (ie, normal BMI, non-smoking, low alcohol intake, adequate leisure-time physical activity, high vegetable intake, high fruit intake, and adequate sleep duration) was associated with a significantly lower risk of depressive symptom. To our knowledge, this is the first prospective cohort study that examined the association between combined healthy lifestyle factors and depressive symptoms in Asia.

Our findings are consistent with those reported in previous studies, which have shown a significant association between combined healthy lifestyle factors and depressive symptoms.<sup>17–23</sup> One such example is Adjibade et al, which showed that participants with five healthy lifestyle factors (ie, never smoking, low alcohol intake, being physical active, having a healthy diet, and healthy BMI) had a significantly lower risk of depressive symptoms compared with those with two or less healthy lifestyle

**Table 4.** The association between alternative versions of the Healthy Lifestyle Index and depressive symptoms

	Healthy Lifestyle Index			P-trend*
	0–2 (low)	3–4 (middle)	5–6 (high)	
HLI without body mass index				
Model 1 <sup>a</sup>	1.00 (reference)	0.85 (0.59–1.22)	0.60 (0.27–1.31)	0.162
Model 2 <sup>b</sup>	1.00 (reference)	0.92 (0.63–1.33)	0.59 (0.26–1.32)	0.264
Model 3 <sup>c</sup>	1.00 (reference)	1.03 (0.67–1.52)	0.85 (0.37–1.97)	0.884
HLI without smoking status				
Model 1 <sup>a</sup>	1.00 (reference)	0.67 (0.47–0.96)	0.55 (0.24–1.26)	0.021
Model 2 <sup>b</sup>	1.00 (reference)	0.68 (0.47–0.98)	0.51 (0.22–1.20)	0.021
Model 3 <sup>c</sup>	1.00 (reference)	0.77 (0.52–1.13)	0.66 (0.27–1.60)	0.146
HLI without leisure-time physical activity				
Model 1 <sup>a</sup>	1.00 (reference)	0.63 (0.43–0.92)	0.56 (0.28–1.12)	0.019
Model 2 <sup>b</sup>	1.00 (reference)	0.65 (0.44–0.97)	0.55 (0.27–1.11)	0.026
Model 3 <sup>c</sup>	1.00 (reference)	0.74 (0.49–1.10)	0.71 (0.34–1.49)	0.168
HLI without alcohol intake				
Model 1 <sup>a</sup>	1.00 (reference)	0.84 (0.59–1.20)	0.68 (0.32–1.44)	0.214
Model 2 <sup>b</sup>	1.00 (reference)	0.86 (0.59–1.26)	0.72 (0.33–1.55)	0.310
Model 3 <sup>c</sup>	1.00 (reference)	0.97 (0.66–1.45)	0.96 (0.43–2.14)	0.883
HLI without vegetable intake				
Model 1 <sup>a</sup>	1.00 (reference)	0.53 (0.36–0.79)	0.38 (0.21–0.69)	<0.001
Model 2 <sup>b</sup>	1.00 (reference)	0.54 (0.36–0.81)	0.37 (0.20–0.69)	<0.001
Model 3 <sup>c</sup>	1.00 (reference)	0.64 (0.42–0.97)	0.44 (0.24–0.84)	0.007
HLI without fruit intake				
Model 1 <sup>a</sup>	1.00 (reference)	0.59 (0.40–0.88)	0.41 (0.22–0.76)	0.002
Model 2 <sup>b</sup>	1.00 (reference)	0.59 (0.39–0.89)	0.40 (0.21–0.76)	0.002
Model 3 <sup>c</sup>	1.00 (reference)	0.71 (0.47–1.09)	0.52 (0.26–1.01)	0.037
HLI without sleep duration				
Model 1 <sup>a</sup>	1.00 (reference)	0.65 (0.45–0.94)	0.70 (0.34–1.40)	0.044
Model 2 <sup>b</sup>	1.00 (reference)	0.65 (0.45–0.95)	0.73 (0.36–1.50)	0.064
Model 3 <sup>c</sup>	1.00 (reference)	0.78 (0.53–1.15)	1.04 (0.49–2.20)	0.474

HLI, healthy lifestyle index.

\*Based on multiple logistic regression analysis incorporating the HLI as a continuous variable.

<sup>a</sup>Adjusted for age (years, continuous), sex (men or women), workplace (A or B), and the omitted HLI component.

<sup>b</sup>Adjusted for variables in model 1, and marital status (married or not), employment status (permanent employee, contract employee, or part-time employee), job grade (low, middle, or high), night or rotating shift work (yes or no), overtime work (<10, 10–29.9, or ≥30 hours/month), and job strain (quartile).

<sup>c</sup>Adjusted for variables in model 2 and CES-D score (continuous) at baseline.

factors in a French web-based prospective cohort.<sup>17</sup> Given that previous studies, except for one cross-sectional study among Chinese college students,<sup>23</sup> focused on Western populations, our prospective study extends the evidence to an Asian population as well as to a working population, which has been under-researched in relation to the association between the HLI and depressive symptoms.

While smoking, alcohol intake, physical activity, and diet were generally employed, several approaches have been used to operationalize the HLI in previous studies (eTable 1). In addition to the above-mentioned variables, BMI was accounted for the HLI construction in certain studies; four previous studies included BMI in their HLI and suggested that BMI is one of the important components of the HLI.<sup>17–19,22</sup> Following these studies and one on investigating the association between BMI and depression in Japan,<sup>40</sup> we incorporated BMI in our HLI. While sleep has not been used widely in the previous studies,<sup>23</sup> we included sleep duration in the HLI given that a meta-analysis<sup>14</sup> and a Japanese nationwide study<sup>41</sup> indicated a significant association between sleep duration and depressive symptoms/depression. Despite heterogeneity in the definition of the HLI, the previous studies and our study showed that combined healthy lifestyles were inversely associated with depressive symptoms, providing robust evidence on the association.

In our analyses for the impact of each component on the association between the HLI and depressive symptoms, we observed a large attenuation when sleep duration, alcohol intake, BMI, leisure-time physical activity, or smoking status were omitted from the original HLI, suggesting the important contribution of these components to the total score. Similarly, Adjibade et al reported an attenuation in the HLI-depressive symptoms association when BMI or smoking was omitted while no measurable attenuation was observed when alcohol intake or physical activity was omitted.<sup>17</sup> One plausible interpretation for the discrepant finding regarding alcohol intake between the two studies is the much lower proportion of excessive alcohol drinkers in Adjibade et al<sup>17</sup> (8.9%) than in the present study (26.8%), reflecting a large difference of male-to-female ratio (ie, the low proportion of males [23.8%] in Adjibade et al<sup>17</sup> and the high proportion of males in our study [89.2%]). In addition, the difference in the proportion of participants with low physical activity between the previous study (23.8%) and our study (64.1%) may explain the inconsistency of the finding regarding physical activity. In our study, the association was not attenuated when we employed the HLI without vegetable or fruit intake, indicating a small impact of these variables on the HLI. This may have been partly due to the low proportion of participants adhering to the recommended intake of vegetable (15.2%) or fruit (17.7%).

Several mechanisms underlying the association between lifestyles and depression have been suggested. For example, it has been documented that how lifestyle factors (eg, diet, physical activity, sleep) influence pathways associated with depression, namely inflammation, neurotransmitter process, oxidative stress and antioxidant defense systems, neuroprogression, hypothalamic-pituitary-adrenal axis, and mitochondrial disturbances.<sup>42</sup> As for BMI, both obesity and underweight may lead to the development of depression via negative effects on self-image or physical health conditions associated with unhealthy body weight.<sup>43</sup> Alcohol intake may underlie neurophysiological and metabolic changes associated with depression.<sup>44</sup> Tobacco

consumption leads to elevated inflammation and oxidative stress due to exposure to chemicals (eg, free radicals, metals, and tars).<sup>45</sup> These mechanisms may have worked together to link the HLI and depressive symptoms in our study.

Major strengths of this study include using a prospective design and controlling for a range of potential confounders, including work-related factors. However, several limitations should be noted. First, the high rate of loss to follow-up (36%) may have introduced bias. We confirmed, however, that there was no substantial difference in the baseline characteristics between those who participated in the follow-up and those who were lost to follow-up (eTable 2). Second, while we adjusted for numerous potential confounders, we could not rule out the possibility that the observed association is due to unmeasured confounders and residual confounding. Third, certain study variables (eg, physical activity, alcohol intake) were self-reported and thus subject to reporting bias. Fourth, participants had to answer a number of questions to construct the HLI. Future research should develop simple and shortened version of the questionnaire to facilitate data collection. Finally, participants were predominantly male employees from a private manufacturing company. Therefore, caution is required in generalizing the findings.

In conclusion, this prospective cohort study suggests the importance of adherence to multiple healthy lifestyles (ie, normal BMI, non-smoking, no or moderate alcohol intake, adequate leisure-time physical activity, high vegetable intake, high fruit intake, and adequate sleep duration) in the prevention of depressive symptoms.

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.2188/jea.JE20190018>.

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When major depression and heart failure (HF) co-occur, as they often do<sup>1,2</sup>, their individual associations with disability are amplified<sup>3</sup>. Successfully treating depression in people with HF is therefore a high priority. Unfortunately, randomized controlled trials (RCTs) have shown that standard antidepressant medications are not superior to placebo for major depression in people with heart failure<sup>4–6</sup>. In contrast, our team recently reported that an integrative intervention based on cognitive behavior therapy (CBT) was more efficacious than usual care (UC) for depression in people with heart failure<sup>7</sup>. Despite this success, about half of the patients assigned to CBT did not fully remit following treatment. The factors which determine whether CBT will be efficacious for a given patient, i.e., moderators of CBTs effects, are not well-established.

The distinction between moderators and general prognostic factors is clinically meaningful<sup>8</sup>. General prognostic factors are related to the course of an outcome (e.g., depression severity over a six-month follow-up period) regardless of treatment assignment. In contrast, moderators are associated with the efficacy of a specific treatment when compared with an alternative. Thus, evidence regarding treatment moderators can help clinicians identify whether a given patient is likely to benefit from a particular treatment. Furthermore, it may be possible to modify certain moderators that predict diminished efficacy in order to prime subgroups of patients for treatment. However, most prior research on moderators of CBT has focused on non-modifiable moderators such as age or sociodemographic factors<sup>9</sup>, and there has been little moderator research specific to CBT in patients with HF. Our prior publication demonstrating CBT's efficacy for patients with depression and HF did not find evidence for moderating effects of sex, race, or antidepressant use<sup>7</sup>.

We therefore performed a wider but targeted search for moderators of CBT's effects in patients with HF. To target this search, we relied on past evidence regarding the role of physical activity as a general prognostic factor in depression. Low activity levels<sup>10</sup> and activity rhythm disruption<sup>11</sup> are known depression risk factors. Among patients given standard psychotherapy, people with lower levels of physical activity tend to experience a worse prognosis over time<sup>12</sup>. However, this prior work did not address whether activity characteristics moderate CBT response, and was limited by reliance on a self-report physical activity measure. There are several other easily obtainable measures of physical functioning and activity including clinic-based test performance measures and objectively measurable activity characteristics (e.g., average activity levels, activity pattern stability, and activity timing). Since these measures can be easily obtained, e.g., from passive accelerometer-based technology, they could be assessed clinically to help guide treatment strategies.

If any aspect of physical functioning in this group (e.g., HF characteristics, clinic-based functional measures, or accelerometry-based measures) moderate CBT's effects, this would highlight the need to address these factors as a part of depression treatment. Therefore, our first aim was to evaluate individual moderator effect sizes. However, individual moderator effects tend to be small and can provide conflicting treatment indications<sup>8</sup>. Past work has shown that combining multiple moderators can yield larger, more clinically meaningful effects<sup>13,14</sup>. Therefore, our second aim was to assess the effect size gains achieved when combining information from multiple individual moderators.

## Methods

### Participants

The methods and major outcomes of the trial were reported in an earlier publication<sup>15</sup>. Briefly, patients with heart failure were enrolled at the Washington University Medical Center in Saint Louis, Missouri between January 4, 2010 and June 28, 2013. Inclusion criteria were: New York Heart Association (NYHA) Class I-III heart failure diagnosed three or more months before screening, current major depressive episode<sup>16</sup>, and a score of 14 or more on the Beck Depression Inventory (BDI-II)<sup>17</sup>. Exclusion criteria were: being unable to participate because of cognitive impairment, frailty, a communication deficit, or a logistical barrier; poor 1-year prognosis due to a noncardiac comorbidity; past month hospitalization; past month, suicidality, psychosis, or substance abuse; and antidepressant initiation in the past eight weeks (patients treated with antidepressants for more than eight weeks were included). Written informed consent was obtained and participants were compensated for participation. The study was approved by the Washington University Medical Center Human Research Protection Office. One hundred fifty-eight participants were randomized. The present analyses include participants who had data on the six-month depression outcomes (n=123) and are further restricted to 94 patients in whom the baseline moderators were measured (as specified below).

### Randomization

Participants were randomly assigned, in a 1:1 ratio, to CBT plus enhanced UC or enhanced UC alone. Randomization was stratified by baseline antidepressant use.

### Interventions

The intervention was described previously<sup>7</sup>. Briefly, both groups received enhanced UC, which consisted of educational materials on HF self-care from the Heart Failure Society of America<sup>18</sup> and the American Heart Association<sup>19</sup>. Educational materials were reviewed on three 30-minute telephone calls with an experienced cardiac nurse conducted over three to four weeks post-randomization. The CBT group additionally received up to six months of treatment following standard CBT manuals<sup>20,21</sup> as well as a supplemental manual on CBT for cardiac patients<sup>22</sup>.

### Outcome measures

Baseline assessments were conducted between February 2010 and April 2013, and follow-up assessments were collected between May 2010 and July 2014. Outcome assessors were blinded to group assignments. The depression outcome was defined as symptom reductions on the BDI-II<sup>17</sup> (defined as six-month scores minus baseline scores; with negative numbers indicating symptom reductions). To clarify the clinical significance of our findings, we also evaluated how the full combined moderator related to remission status at six months (defined as a score of nine or less on the second version of the Beck Depression Inventory (BDI-II)<sup>15,17</sup>.

## Potential moderators

All moderator measures were assessed at baseline. New York Heart Association (NYHA) class I-II vs. III was used to assess the severity of HF symptoms and left ventricular ejection fraction (LVEF) obtained from echocardiography was used as an index of left ventricular function. Physical functioning was measured as the PROMIS Physical Functioning score<sup>23</sup> and distance (in feet) walked on the 6-minute walk test<sup>24</sup>.

Participants also wore tri-axial accelerometers (Philips Respironics Inc., Murrysville, PA) at baseline to collect minute-by-minute activity counts for one week. We applied both nonparametric<sup>25</sup> and extended-cosine<sup>26</sup> methods to quantify activity characteristics. From the nonparametric measurements, we assessed the level of activity (the average amount of activity during the most active ten hours or M10), rhythm strength (the relative amplitude or RA defined as the difference, between the average levels of activity during the most active 10 hours of the day and the least active 5 hours of the day, standardized to overall activity level), rhythm stability (interdaily stability or IS defined as the ratio of variability within the mean 24-hour activity profile to the overall activity variability), and rhythm fragmentation (intra-daily variability or IV defined as the ratio of the hour-to-hour activity variability to the overall activity variability). We also used a sigmoidally transformed cosine curve to estimate alpha (a parameter indicating the relative width of active to rest periods with higher values indicating more narrow active relative to resting periods) and two timing parameters (reflecting the times when activity levels pass through the middle level of the estimated model when the participant “gets going” (up-mesor) and “settles down” (down-mesor)).

We analyzed actigraphy data only from adequate recordings defined as those with a duration of at least 72 hours of data; 18 recordings did not meet this criterion (analytic sample reduced to n=105). Extended cosine modeling did not converge for an additional eight patients who were therefore excluded (analytic sample reduced to n=97). Of these participants with complete outcome and actigraphy data, three did not have data from the walk test and were excluded. The resulting 94 patients who were included did not differ from those missing moderator measures in terms of gender (Chi square test p=0.40), treatment assignment (Chi square test p=0.75), baseline depression (Chi square test p=0.30), symptom changes (T-test p=0.10), or remission status (Chi square test p=0.27).

## Statistical analysis

We computed individual moderator effect sizes and 95% confidence intervals (CIs) using bootstrapping<sup>8</sup>. Effect sizes are based on Spearman correlations, with more positive values indicating that greater values of the moderator are associated with less benefit of CBT over UC; more negative values indicating that greater values of the moderator are associated with more benefit of CBT versus UC.

Next, we assessed moderator effect sizes when combining clinic-based measures, accelerometer-based measures, or both. Only measures with individual moderator effect sizes of  $|0.10|$  were considered potentially relevant and included the combined moderator models. The combined moderator method derives optimal weights for each moderator through a LASSO regression, which allows for correlated variables without overfitting<sup>27</sup>.

LASSO weights are extracted and applied to the original data to compute a combined moderator. We then estimated the combined moderator effect sizes (95% CI). To illustrate the combined moderator effects, we plotted the combined moderators against the predicted level of depressive symptom change in each of the treatment arms. To assess how the full combined moderator related to remission, we calculated the odds of remission given CBT (vs. UC) in people who were above and below the “cross-point” (see below). These odds ratios were calculated using logistic regression adjusted for age, sex, and antidepressant use. For all analyses, continuous variables were standardized to a mean of 0 and standard deviation of 1.

## Results

### Individual moderators effect sizes (Table 2 and Figure 1):

The absolute values of the individual moderator effect sizes were small (range:  $r=0.00$  to  $0.21$ ). The largest moderator effect sizes from the clinic-based measures were percent LVEF and NYHA class III vs. I/II. Lower LVEF values, indicating worse cardiac contractile function, were associated with a greater effect of CBT vs. UC on depression symptom change. Patients in NYHA class III, indicating more severe heart failure symptoms (vs. NYHA grades I/II), also benefited more from CBT.

Of the actigraphy variables, interdaily stability, alpha, and down-mesor had the largest moderating effects. More regular activity patterns across days (higher interdaily stability) was associated with a greater effect of CBT. Having narrower active periods (higher alpha) was associated with less benefit from CBT. Later evening settling times (later down-mesor) was associated with a greater effect of CBT.

### Combined moderator effect sizes (Table 2 and Figure 2):

When combining the moderators within the clinic and actigraphy variable sets (separately) effect sizes were still small. In contrast, the full combined moderator that included both clinic-based and actigraphy measures yielded a medium moderator effect size.

### Relationship between the full combined moderator and remission:

We stratified patients depending on whether they were above or below point where the lines cross in the full combined moderator (right of Figure 2; above the cross-point, the effects of CBT and UC are similar, whereas below the cross-point CBT is associated with larger symptom reductions). In patients below this cross-point (76% of the sample), CBT was associated with a greater likelihood of remission when compared with UC (see Figure 3); in this subset of patients, the odds ratio for remission for CBT vs. UC was 5.0 (95% confidence interval: 1.78, 14.1;  $p=0.002$ ). In contrast, in the 25% of patients who were above this cross-point, remission rates were similar in the CBT and UC arms; in these patients, the odds of remission for CBT vs. UC was 0.88 (95% confidence interval: 0.11, 6.93;  $p=0.90$ ).

## Discussion

Consistent with other studies<sup>13,14</sup>, we observed that the moderating effects of individual patient characteristics were generally small. However, combining information from individual variables yielded a moderate effect size and identified a subgroup of patients who were unlikely to remit regardless of whether they were provided with CBT or UC alone (Figure 2). Pending replication, these clinical and actigraphy variables could be routinely assessed prior to treatment and combined to assess the likelihood that any given patient will benefit more from CBT than UC. When treating patients with high combined moderator scores, clinicians could consider the factors that led to high combined moderator values, and explicitly address them during treatment. We are not suggesting that, in practice, CBT should be withheld from patients with high moderator scores; rather, we propose that it may be possible to pre-empt non-response to CBT by identifying patients who are less likely to benefit and then addressing barriers to treatment success early on.

Surprisingly, we found that the benefit of CBT vs. UC was larger in patients with indicators of more severe HF. In contrast to the medical prognosis for patients with HF and reduced ejection fraction, the prognosis for patients who have HF with preserved ejection fraction has not improved in recent decades<sup>28</sup>. HF with preserved ejection fraction may have a more complex pathophysiology that may be more challenging to treat<sup>29</sup>. Thus, patients who had a reduced ejection fraction may have experienced less uncertainty, frustration, or disappointment with the medical management of their heart failure, whereas difficulties managing HF with preserved ejection fraction may have contributed to a lack of benefit when provided CBT. Although empirically testing this explanation represents a next step outside the scope of this work, our novel findings suggest that future studies and treatments may need to consider the trajectories of physical health a potential barrier or facilitator of depression remission in patients with HF.

Our second set of findings pertained to baseline physical activity variables that are associated with CBT's efficacy. We found that the effect of CBT over UC was smaller in patients who had less stable activity patterns and narrower active periods at baseline, likely due to earlier evening settling. These activity characteristics have been previously associated with depression symptoms, e.g., studies examining the stability of activity patterns across days<sup>30,31</sup> and the active period length<sup>31–34</sup>. Unstable activity patterns and narrower active periods may reflect less regular and consistent engagement with rewarding social and leisure-time activities. Unstable activity patterns could also reflect the burden of comorbidities or circadian misalignment (e.g., poor coordination between the timing of biological and/or psycho-behavioral processes). Future work is needed to clarify why these aspects of activity patterns are associated with depression<sup>30–34</sup> and a lack of benefit when given CBT vs. UC. Prior research has shown that bright light therapy<sup>35,36</sup> and exercise<sup>37</sup> can stabilize activity rhythms, and it is plausible that activity planning occurring in CBT could deliberately prolong the active period. Future work will need to test whether adjunctive or primer treatments (e.g. home-based cardiac rehabilitation) aimed at stabilizing activity patterns and prolonging the active period can facilitate greater CBT efficacy.

Several limitations should be noted including, as stated above, our inability to specify precisely why these factors predict greater or lesser CBT efficacy. In addition, our sample size was relatively small and we did not have adequate statistical power to detect small moderation effects. We focused on effect sizes rather than p-values; however, given that this is the initial work examining the moderating role of activity characteristics, our findings must be validated before clinical implementation. Another potential limitation is that this trial was conducted in a specialty care setting; as such, our findings may not generalize to primary care settings where other moderators may emerge.

Despite these limitations, our study has several strengths. First, we used a randomized controlled trial to identify moderators of an established, but not uniformly efficacious, treatment in an chronically ill patient population. Second, we assessed clinical and actigraphy-based variables that are at least theoretically feasible to routinely assess in this clinical context. Third, using a combined moderator methodology rendered a more meaningful (larger) effect size and identified a group in whom CBT and UC were equally efficacious.

In conclusion, we have demonstrated the utility of the combined moderator approach and identified objectively measurable factors that could be addressed to clarify why CBT is more efficacious for some patients with major depression and HF than it is for others. Our findings regarding the severity of heart failure highlight the need for psychological treatments to acknowledge the challenges facing patients who have heart failure with preserved ejection fraction. We also generated initial evidence regarding which baseline activity characteristics that are relevant to CBT's efficacy. These moderating patient characteristics that apparently detract from/are required for CBT's efficacy should be addressed in future work. Potentially, considering and/or modifying these pre-treatment moderators could better prepare patients for success in CBT.

### Conflict of Interest and Source of Funding:

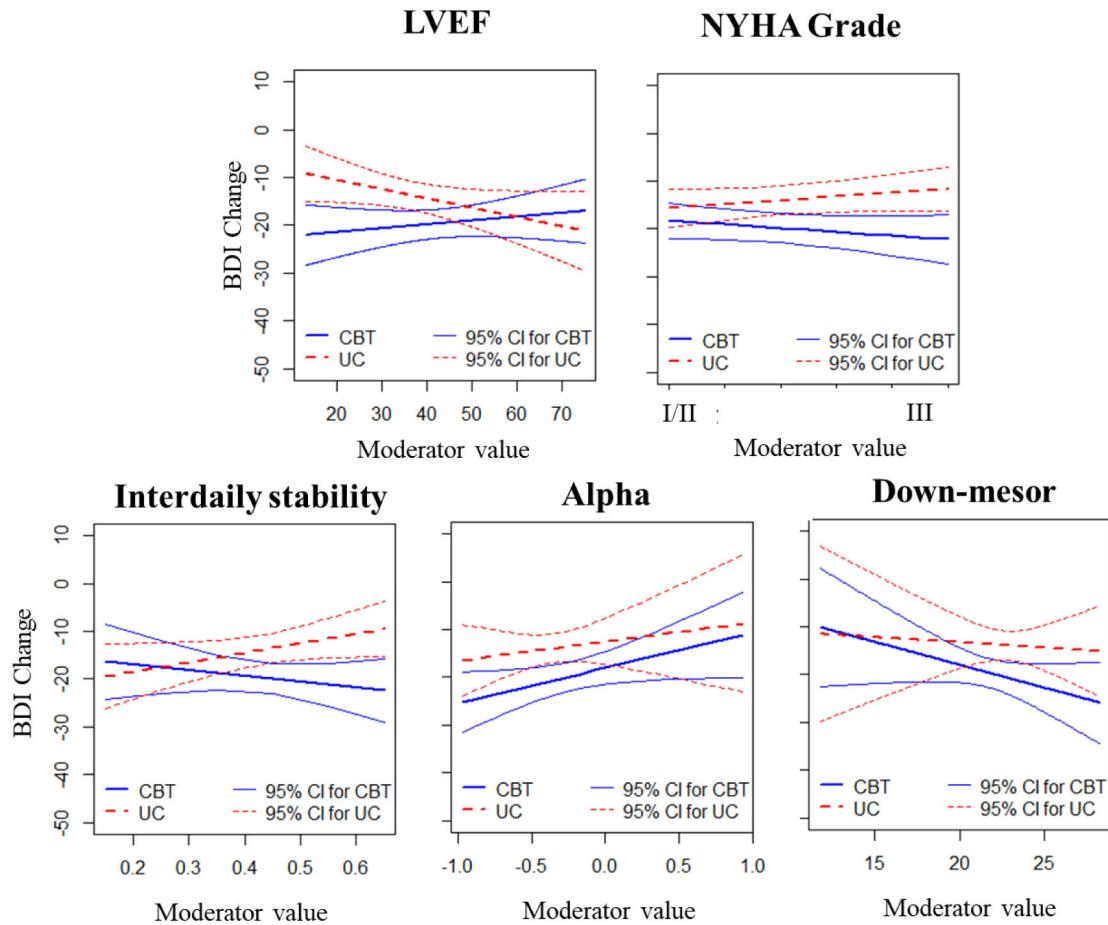
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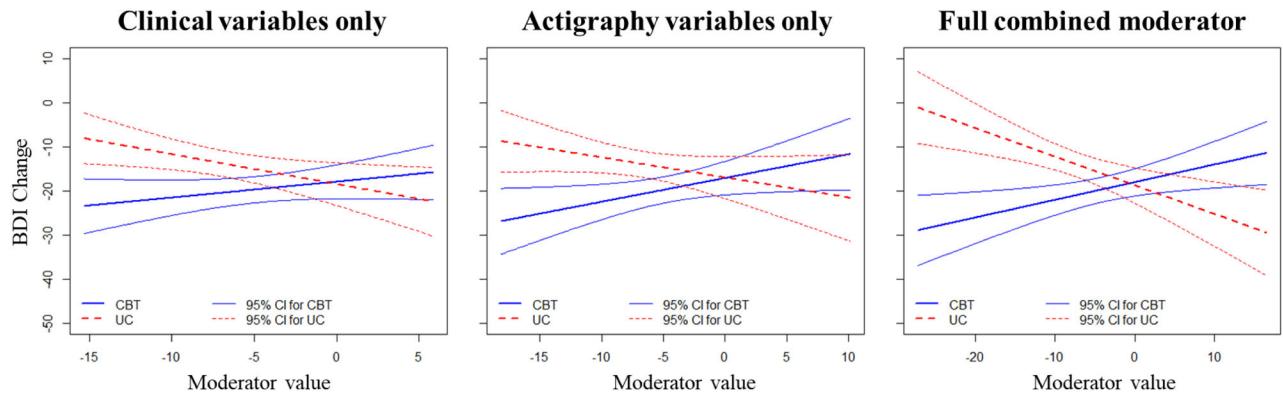
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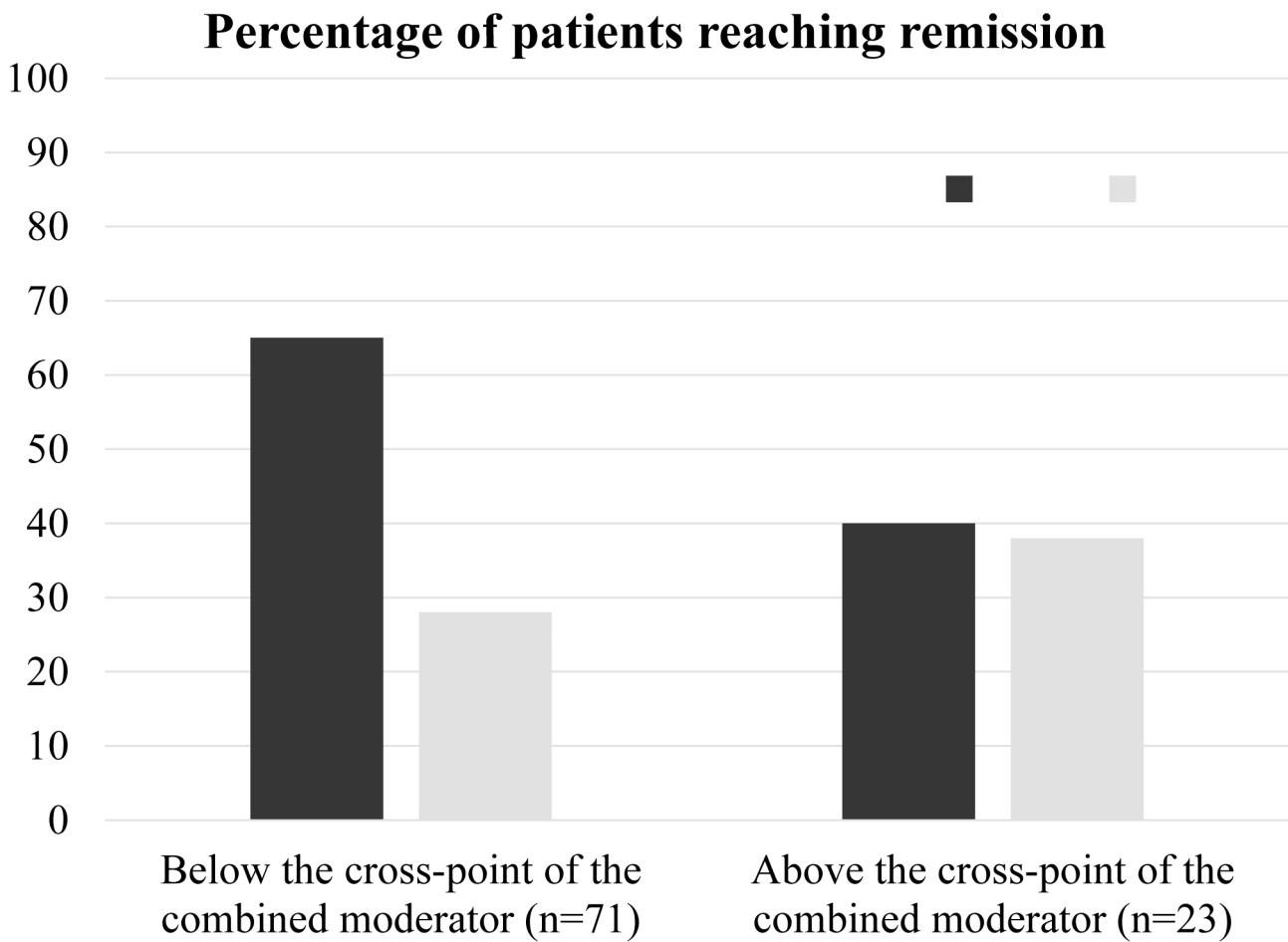
**Figure 1. Average depression symptom changes in the two treatments depending on the value of the individual moderators.**

Note the difference between the two treatment arms in terms of the level of depression symptom changes varies across the moderator values, e.g., there is less overlap between the two lines at lower values of LVEF and higher values NYHA grades.



**Figure 2. Average depression symptom changes in the two treatments depending on the value of the combined moderators.**

Note that CBT-UC separation is greatest at lower values of the full combined moderator.



**Figure 3. Remission rates stratified by treatment arm and the cross-point of the full combined moderator.**

**Table 1.**

Baseline descriptive information from the analytic sample

	<b>CBT (n=46)</b>	<b>UC (n=48)</b>
Age	58 (11)	58 (11)
Female, % (n)	52 (24)	46 (22)
Baseline BDI-II	30 (7)	30 (9)
BDI-II change (6 month-baseline)	-20 (11)	-14 (10)
Remission, % (n)	56 (26)	29 (14)
<b>Potential moderators</b>		
PROMIS Physical Function	37 (7)	35 (6)
6-minute walk test distance (feet)	1006 (391)	988 (444)
Percent LVEF	43 (17)	37 (15)
NYHA Grade III	35 (16)	44 (21)
Average activity during the most active 10 hours	208 (91)	238 (115)
Relative amplitude	0.8 (0.1)	0.9 (0.1)
Interdaily stability	0.4 (0.1)	0.4 (0.1)
Intradaily variability	1 (0.3)	1 (0.3)
Alpha (relative narrowness of active period)	-0.2 (0.4)	-0.3 (0.3)
Up-mesor	8 (3)	8 (2)
Down-mesor	22 (3)	23 (2)

Means and standard deviations shown unless otherwise noted; remission is defined as Beck Depression Inventory (BDI-II) scores of nine or less at the six-month follow-up

**Table 2.**

Individual and combined moderator effect sizes (n=94)

Individual moderator effect sizes (95% Confidence Interval)	
	BDI Change
PROMIS Physical Function	0.01 (-0.16, 0.19)
6-minute walk test distance (feet)	0.05 (-0.14, 0.23)
<b>LVEF, %</b>	<b>0.18 (0.01, 0.37)</b>
<b>NYHA Grade III vs. I/II</b>	<b>-0.19 (-0.37, 0.02)</b>
Average activity during the most active 10 hours (M10)	0.00 (-0.21, 0.18)
Relative amplitude	-0.09 (-0.28, 0.08)
<b>Interdaily stability</b>	<b>-0.21 (-0.39, -0.03)</b>
Intradaily variability	0.00 (-0.19, 0.22)
<b>Alpha (relative narrowness of active period)</b>	<b>0.13 (-0.07, 0.34)</b>
Up-mesor	0.03 (-0.15, 0.22)
<b>Down-mesor</b>	<b>-0.10 (-0.31, 0.08)</b>
Combined moderator effect sizes (95% CI)	
1. Clinical variables (LVEF % and NYHA class)	0.26 (0.08, 0.44)
2. Activity rhythm variables (interdaily stability, alpha, and down-mesor)	0.26 (0.05, 0.45)
3. Both clinical and activity rhythm sets (1 and 2 combined)	0.38 (0.20, 0.52)

Positive moderator effect sizes indicate that, as the value of the moderator goes up, the effect of CBT (vs. UC) is smaller; negative moderator effect sizes indicate that, as the value of the moderator goes up, the effect of CBT (vs. UC) is greater. Bold indicates the individual variable was selected into the combined moderator based on having an effect size of >0.10.

counterparts [10], and all time-domain measures of HRV, including root mean square of the successive differences (RMSSD), were lower in patients with major depression [11]. Finally, in a sample of physically healthy, unmedicated patients, RMSSD was significantly reduced in those with major depressive disorder (MDD) versus a control group [7].

Numerous mechanisms that explain the association between HRV and depressive symptoms have been theorized. In healthy samples with MDD, autonomic dysregulation, either deficient parasympathetic modulation or predominant adrenergic activation, has been found [10]. Parasympathetic nervous system activation is thought to be influenced by mood states and to become increasingly dysfunctional during longer-term depression [12]. In patients with MDD, Borrione and colleagues [13] found that decreased HRV was associated with specific depressive symptoms, such as guilt, loss of pleasure in activities, and psychomotor retardation. In a study examining two samples of healthy young adults, the association between depressed mood and low HRV was mediated by habitual dietary patterns and disinhibited eating behaviors, respectively [14]. Additionally, although the association between depression and HRV was once thought to be driven by antidepressant medications [15–17], a recent study has demonstrated the association is exhibited without the effect of antidepressant medication [18].

With regard to cardiac samples, the association between depression and HRV may be partially related to reduced physical activity and physical fitness. In a large prospective study following patients with stable coronary heart disease, the occurrence of cardiac events was higher among those endorsing more depressive symptoms in comparison to those with fewer depressive symptoms; the relationship between cardiac events and depression in patients was largely explained by physical inactivity [19]. Furthermore, in another prospective study following patients who were hospitalized for cardiac-related emergencies, physical inactivity was one of the factors (in addition to patient comorbidity and disability) that accounted for higher rates of mortality among those with MDD [20]. Thus, physical inactivity has demonstrated a strong association with poor outcomes in those with cardiovascular disease. However, the role of physical fitness in the relationship between HRV and depression has not been evaluated in HF patients.

Depressive symptoms and fitness are critically linked, and physical fitness is known to be lower in healthy individuals diagnosed with depression [21]. Cardiorespiratory fitness, and not obesity or higher weight, predicted onset of depressive symptoms in a large, diverse sample [22]. Additionally, maintenance of cardiorespiratory fitness appears to be protective against

incidence of depression complaints to physicians [23], and higher cardiorespiratory fitness was associated with a lower risk of incidence of depressive symptoms in a longitudinal study [24]. Thus, fitness is clearly associated with depression and may be mechanistic in the association between depression and HRV, particularly in HF patients. In HF, depression is associated with reduced physical activity [25], which likely leads to reduced physical fitness. Physical fitness may be especially important in HF patients given the severe decompensation of the cardiovascular system. In patients with coronary artery disease, poorer cardiopulmonary fitness was associated with more depressive symptoms [26]. Further, another study demonstrated that improvements in cardiopulmonary fitness during cardiac rehab were associated with a reduction in depressive symptoms [27].

Hughes and colleagues [28] explored the association between depression and physical activity and fitness in a small sample of cardiac rehabilitation patients. Depressed patients were matched with nondepressed controls (22 patients in each group), and both frequency- and time-domain HRV measures were obtained over a 24 hr ambulatory recording period. Depression was significantly associated with HRV measures, and both physical activity and fitness were lower in the depressed patients [28]. HRV indices significantly associated with depression included total frequency power, ultra-low-frequency power, low-frequency power, standard deviation of N-N intervals (SDNN), and standard deviation of the 5 min average of N-N intervals (SDANN) [28]. The association between HRV and depression was attenuated by including physical activity and fitness in the model [28]. Thus, poorer fitness and lower levels of physical activity accounted for altered autonomic function in the sample of depressed cardiac patients. At that time, HF was not an approved indication for cardiac rehabilitation, although some patients in the sample may have had HF comorbid with their qualifying diagnosis (e.g., myocardial infarction). Thus, the application and validity of this association in HF patients needs to be explored.

In sum, depression has been shown to predict mortality in HF [29] and a likely mechanism is reduced HRV. Determining if physical fitness helps account for the association between reduced HRV and depressive symptoms in HF could have important clinical implications. Previous studies have investigated other cardiac samples but not specifically HF patients. The current study sought to examine the association between depressive symptoms and HRV in a sample of HF patients and to extend the findings of Hughes and colleagues [28] and Whooley and colleagues [19]. It was hypothesized that depressive symptoms and HRV would be inversely associated in HF patients and physical fitness would attenuate this association.

## Methods

### Sample/Setting

This cross-sectional study was a secondary analysis of a large-scale nonrandomized clinical trial investigating cognitive performance in HF older adults. The current study included 125 HF patients and was a secondary analysis of a larger National Institutes of Health (NIH) funded study, for which study design and results are published elsewhere [25]. The Cognitive Benefits of Cardiac Rehabilitation in People with Heart Failure (CHF CaRe) study (Trial Identifier: NCT00871897) was a prospective cohort study of patients with HF. The primary aim of the parent study was to examine the impact of cardiac rehabilitation on cognitive function in HF patients.

In the parent study, HF patients were eligible for inclusion if they were English speaking, between 50 and 85 years old, and had been diagnosed as New York Heart Association (NYHA) class II or III. Exclusion criteria for the parent study included having a history of neurological injury or disorder (e.g., dementia, stroke), a moderate to severe head injury (i.e., losing consciousness for more than 10 min), a history of or current severe mental illness (e.g., schizophrenia, bipolar disorder), a history of drug or alcohol abuse, sleep apnea that has not been treated, or renal failure that necessitated dialysis.

### Procedure

The Institutional Review Boards (IRBs) of Kent State University and Summa Health System approved the study protocol. CHF CaRe enrolled patients recruited from the Summa Health System in Akron, Ohio, where research activities were conducted. Both HF patients who were enrolled in a 12 week cardiac rehabilitation program and those who were not participating in a cardiac rehabilitation program attended study visits on three occasions (baseline, Week 12, and Month 12). During study visits, HF patients participated in neuropsychological assessments, blood pressure and heart rate measurements, a walking exercise test, and questionnaires assessing diet, physical activity, and stress levels. Additionally, participants completed questionnaires and returned them via mail at Months 6 and 9. Participants provided informed written consent prior to enrollment.

## Measures

### Depressive Symptoms

Depressive symptoms were assessed with the Beck Depression Inventory (BDI)-II [30]. Total BDI-II scores

range from 0 to 63, with higher scores indicating greater depressive symptomology. A score of 0–13 is in the minimal range, 14–19 is mild, 20–28 is moderate, and scores between 29 and 63 are considered severe. The BDI-II demonstrates strong psychometric properties, with good reliability ( $r = .93$  to  $.96$ ) and internal consistency ( $r = .54$  to  $.74$ ) in medical patients [31]. Cronbach's  $\alpha$  was .92 for BDI-II items in this sample.

### Physical Fitness

Physical fitness was assessed via the 2 min step test (2MST), which evaluates aerobic endurance in a limited space and is an effective tool for HF patients [32]. During the 2MST, participants were asked to march in place for 2 min, lifting knees to a target marked on the wall, at the midpoint between the kneecap and crest of the iliac. The total number of times the right knee met the target was counted; the higher the step count, the greater the amount of physical fitness indicated [32]. Normal step count for elderly (aged 60–84) women and men ranges from 60 to 107 and 71 to 115, respectively [32]. In this sample, there was a significant difference between class II HF patients ( $M = 65.54$ ,  $SD = 23.82$ ) and class III HF patients ( $M = 43.13$ ,  $SD = 26.78$ ) on 2MST scores,  $t(104) = 2.536$ ,  $p = .013$ , indicating that those with more severe HF had significantly worse aerobic endurance.

### Heart Rate Variability

Participants underwent a laboratory protocol in which resting HRV was collected to quantify autonomic nervous system function. A Hutcheson Impedance Cardiograph with a clinical-grade electrocardiogram (ECG; Model HIC-2500, Bio-Impedance Technology, Chapel Hill, NC) was used, and ECG signals were continuously sampled at 500 Hz using three disposable electrodes placed in a lead-II configuration [33]. During the laboratory protocol, participants were continuously monitored for a 10 min resting period while seated in standard room temperature. To ensure optimal placement of electrodes and adaptation to the protocol prior to assessment, a 1 min minimum test recording was obtained.

Generated R-R interval data were imported into Kubios version 2.1 (Biosignal Analysis and Medical Imaging Group, Kupio, Finland) for analysis. A trained research team member manually edited ECG data for electrical interference and artifact. Recordings shorter than 3 min in length were excluded from final analyses, as short epochs can result in estimates of HRV that are not comparable with longer (e.g., 10 min) recordings. The 3 min recording minimum was chosen as the cutoff to preserve as much data as possible for analysis. The interpolation rate was 4 Hz and no trend removal was

used. For the present study, the time-domain component of HRV, RMSSD, generated by Kubios was used in analyses, as it has been shown to be one of the most important HRV measures for HF patients [34] and is suitable for short-term ECG recordings [35]. Additionally, high-frequency (0.15–0.40 Hz), low-frequency (0.04–0.15 Hz), and total power HRV components were generated by Kubios. All HRV variables were highly correlated ( $r = .82$  to  $.94$ ), and results for each were significant and comparable to the findings for RMSSD. For simplicity, only results regarding RMSSD are reported.

### Demographic, Medical, and Psychosocial Variables

Self-reported demographic and clinical variables examined in this sample included: sex (0 = female, 1 = male), age (years), ethnicity (Caucasian = 1, Hispanic/Latino = 2, Asian American = 3, African American = 4, Native American/Alaskan Eskimo = 5, Mixed = 6), education (years completed),  $\beta$ -blocker use, hypertension (0 = not present, 1 = present), and diabetes mellitus (0 = not present, 1 = present). Severity of HF was determined by inquiring about participants' current limitations and symptoms, and responses were used to categorize HF severity as NYHA class I, II, III, or IV [36].

### Statistical Analysis

Descriptive statistics (e.g., means, standard deviations, frequencies) were generated for sample characteristics. Before testing study hypotheses, data were inspected for violations of hierarchical multiple regression assumptions (e.g., distributional normality, homogenous error variance). RMSSD was log-transformed to ensure data were normally distributed (skewness  $<3$  and kurtosis  $<10$ ); no additional violations of assumptions were evident. Two hierarchical multiple regressions were performed to examine the relationships between depressive symptoms, physical fitness, and HRV (RMSSD) in HF patients. Missing data were handled using listwise deletion based on missing HRV data, as most missing data were due to problematic ECG recordings in this sample. The parent study included 226 participants; after HF patients with missing HRV data were excluded, the total sample size was 125. The statistical significance criterion was set at  $p < .05$ .

In both regression analyses, demographic and medical covariates were controlled for in the first block entered. In the first regression analysis, Block 1 comprised demographic and medical variables, including sex, age,  $\beta$ -blocker use, hypertension, and diabetes. Block 2 included BDI-II scores to assess the incremental predictive validity of depressive symptoms. In the second regression analysis, Block 1 included the same

demographic and medical variables. In Block 2, 2MST scores were entered, and Block 3 included BDI-II scores. Log-transformed RMSSD scores were used as the dependent variable for both regression analyses. All analyses were conducted using IBM SPSS version 24.

### Results

The sample consisted of 125 HF patients. The sample was predominately male (68.8%) and Caucasian (83.2%). Most participants had NYHA class II HF (88.9%), and approximately 26% of patients had some type of implantable cardiac device (see Table 1). No patients in this sample had diastolic dysfunction. Average depressive symptoms on the BDI-II were 8.14 ( $SD = 8.12$ ), and the mean for RMSSD scores was 36.93 ( $SD = 55.47$ ). Four percent of the sample identified experiencing severe depressive symptoms (BDI-II scores of 29–63) and 5.6% reported experiencing moderate depressive symptoms (BDI-II scores of 20–28). Regarding 2MST scores, 55.3% of men and 55.6% of women demonstrated physical fitness scores below their respective normal ranges. Additional demographic and medical characteristics are presented in Table 1. Cardiac medications used by this sample can be found in Table 2. Small correlations emerged between RMSSD and age ( $r = .20, p < .05$ ) and RMSSD and BDI-II scores ( $r = -.18, p < .05$ ). A small, negative association between 2MST and BDI-II scores was also significant ( $r = -.20, p < .05$ ). Correlations between all primary variables are presented in Table 3.

Two hierarchical multiple linear regressions were conducted to examine the relationship among BDI-II scores, 2MST scores, and RMSSD. In the first regression, Block 1 contained demographic and medical control variables (sex, age,  $\beta$ -blocker use, hypertension, and diabetes) and did not significantly predict RMSSD. In Block 2, adding BDI-II scores improved model fit,  $\Delta F(7,92) = 7.54, \Delta R^2 = .06, p < .01$ . Controlling for sex, age,  $\beta$ -blocker use, hypertension, and diabetes, higher BDI-II scores significantly predicted lower RMSSD,  $\beta = -.26, p < .01$  (see Table 4).

2MST was added to the model to assess the incremental predictive value of depressive symptoms after controlling for demographic and medical control variables, as well as 2MST scores. Controlling for 2MST, BDI-II remained a significant predictor of RMSSD,  $\beta = -.29, p < .01$ . No relationship emerged between 2MST scores and RMSSD,  $p > .05$  (see Table 5).

Primary analyses were also tested in a moderation framework and results largely replicated regression analyses. Physical fitness (2MST) was examined as a moderator of the relation between BDI-II and HRV. BDI-II and 2MST were centered and entered in the

**Table 1.** Demographic and clinical characteristics of sample ( $N = 125$ )

	$M \pm SD$ or $N (\%)$
Age (years) <sup>a</sup>	$68.55 \pm 8.92$
Male	86 (68.8%)
Caucasian	104 (83.2%)
Education (years) <sup>a</sup>	$13.53 \pm 2.61$
Married <sup>a</sup>	84 (67.7%)
Diabetes (no = 0; yes = 1) <sup>a</sup>	46 (37.1%)
Hypertension (no = 0; yes = 1) <sup>a</sup>	83 (66.9%)
Heart attack (no = 0; yes = 1) <sup>a</sup>	70 (56.5%)
Bypass valve replacement surgery (no = 0; yes = 1) <sup>a</sup>	42 (33.9%)
High cholesterol (no = 0; yes = 1) <sup>a</sup>	82 (66.1%)
Thyroid problems (no = 0; yes = 1) <sup>a</sup>	30 (24.2%)
Ejection fraction <sup>b</sup>	$42.19 \pm 14.48$
Device <sup>c</sup>	
Pacemaker	13 (10.7%)
ICD	11 (9.0%)
Combination	8 (6.6%)
New York Heart Association class <sup>b</sup>	
Class I	0 (0%)
Class II	104 (88.9%)
Class III	12 (10.3%)
Class IV	1 (0.9%)
RMSSD	$36.93 \pm 55.47$
Low-frequency HRV	$614.58 \pm 1846.16$
High-frequency HRV	$1139.17 \pm 4455.46$
2MST <sup>d</sup>	$63.04 \pm 24.92$
Depressive symptoms (BDI-II) <sup>e</sup>	$8.14 \pm 8.12$

Means and standard deviations are presented for continuous variables. Sample size and percentages are presented for categorical variables. RMSSD, low-frequency HRV, and high-frequency HRV represent raw values in milliseconds.

*BDI* Beck Depression Inventory; *HRV* heart rate variability; *ICD* implantable cardioverter defibrillator; *RMSSD* root mean square of successive differences; *SD* standard deviation.

<sup>a</sup> $n$  of 124.

<sup>b</sup> $n$  of 117.

<sup>c</sup> $n$  of 122.

<sup>d</sup> $n$  of 113.

<sup>e</sup> $n$  of 123.

second step of the regression analysis (covariates entered in first step). Prior to entering the interaction term, only BDI-II was a significant, unique predictor of HRV [ $\beta = -.29$ ,  $t(92) = -2.79$ ,  $p = .007$ ]. In the third step, the interaction term did not explain significant variance. Thus, 2MST was not a significant predictor of the relation between the BDI-II and HRV; results support the assertion that physical fitness does not attenuate the association between depressive symptoms and HRV.

**Table 2.** Cardiac medication use of sample ( $N = 108$ )

	$N (\%)$
ACE inhibitors	63 (58.3%)
ARBs	12 (11.1%)
Aspirin	77 (71.3%)
Beta blockers	74 (68.5%)
Calcium channel blockers	10 (9.3%)
Diuretics	56 (51.9%)
Inotropes	7 (6.5%)
Nitrates	6 (5.6%)
Plavix	44 (40.7%)
Statins	47 (43.5%)

*ACE* angiotensin converting enzyme; *ARBs* angiotensin II receptor antagonists.

**Table 3.** Bivariate correlations between primary variables and demographic, medical, and psychosocial variables

Variable	1	2	3	4	5	6
1. Sex	—					
2. Age	.15	—				
3. Hypertension	-.14	.06	—			
4. Diabetes	-.06	-.15	.25**	—		
5. BDI-II	-.20*	-.20*	.10	.01	—	
6. 2MST	.17	-.14	-.19*	-.17	-.20*	—
7. RMSSD	-.09	.20*	.02	-.22*	-.18*	.00

2MST 2 min step test; *BDI* Beck Depression Inventory; *RMSSD* root mean square of successive differences.

\* $p$ -value  $<.05$ ; \*\* $p$ -value  $<.01$ .

## Discussion

In this sample of HF patients, depressive symptoms and HRV were negatively associated. In contrast to findings in other samples of cardiac patients, physical fitness did not attenuate the association between HRV and depressive symptoms. Thus, results in this sample of HF patients do not corroborate previous findings [19, 28].

Physical activity is a multidimensional construct that involves numerous kinds of behavior and varies on a day-to-day basis, making it difficult to reliably measure [37]. Fitness, which is construed as a capacity measure and was used in this study, can be assessed with more reliability and accuracy [37]. Indeed, cardiorespiratory fitness and physical activity levels are considered independent risk factors for cardiovascular diseases [38]. For example, greater cardiorespiratory fitness is associated with fewer CVD risk markers [39] and lower incidence of hypertension [40], and healthy individuals with greater cardiorespiratory fitness have exhibited lowered risk for CVD [41].

**Table 4.** Association of depressive symptoms (BDI-II) with RMSSD in heart failure patients

	B (SE b)	t	$\beta$
Block 1			
Sex	−0.33 (0.21)	−1.57	−.15
Age	0.02 (0.01)	1.97	.19
B-blocker	0.40 (0.21)	1.95	.19
Hypertension	0.04 (0.20)	0.17	.02
Diabetes	−0.34 (0.20)	−1.71	−.17
$R^2$	0.10		
F	2.29		
Block 2			
BDI-II	−0.03 (0.01)**	−2.75	−.26
$\Delta R^2$	0.06**		
F for $\Delta R^2$	7.54**		

Sex: male = 1, female = 2;  $\beta$ -blocker use: no = 0, yes = 1; hypertension: no = 0, yes = 1; diabetes: no = 0, yes = 1.

BDI Beck Depression Inventory; RMSSD = root mean square of successive differences.

\*\*p-value <.01.

**Table 5.** Association of physical fitness (2MST) and depressive symptoms (BDI-II) with RMSSD in heart failure patients

	B (SE b)	t	$\beta$
Block 1			
Sex	−0.26 (0.21)	−1.21	−.13
Age	0.02 (0.01)	1.87	.19
B-blocker	0.29 (0.21)	1.39	.14
Hypertension	0.08 (0.20)	0.38	.04
Diabetes	−0.30 (0.20)	−1.51	−.15
$R^2$	0.08		
F	1.66		
Block 2			
2MST	0.00 (0.00)	−0.22	−.02
$\Delta R^2$	0.00		
F for $\Delta R^2$	0.05		
Block 3			
BDI-II	−0.03 (0.01)**	−2.79	−.29
$\Delta R^2$	0.07**		
F for $\Delta R^2$	7.76**		

Sex: male = 1, female = 2;  $\beta$ -blocker use: no = 0, yes = 1; hypertension: no = 0, yes = 1; diabetes: no = 0, yes = 1.

2MST 2 min step test; BDI Beck Depression Inventory; RMSSD root mean square of successive differences.

\*\*p-value <.01.

Whooley and colleagues [19] used a measure of physical activity, which may partially explain discrepant findings. Alternatively, Hughes and colleagues [28] included physical fitness and demonstrated attenuation

of the association between HRV and depression in a cardiac sample. However, that study examined cardiac rehabilitation patients, which included post-myocardial infarction and post-cardiac event patients but not necessarily HF patients. Thus, the different findings regarding physical fitness may be specific to the inclusion of HF patients in this sample. Additionally, results of the current study may be limited due to range restriction in variability of HRV scores, as suppressed HRV in HF is common. Therefore, findings may be distorted and should therefore be interpreted with caution. Furthermore, no distinction between cognitive and somatic symptoms was made during analyses in this sample, which could be problematic as patients with somatic complaints specific to a medical condition can be confused with depressive symptoms [42]. Thus, some depressive symptoms reported by HF patients may be attributable to symptoms caused by HF. Additionally, in this sample, only a small proportion of patients reported clinically significant depressive disorders. Further, although the BDI-II has demonstrated validity and reliability [31], results may have varied if a different measure of depression or clinician diagnosis were used instead.

In HF, chronic alterations of the autonomic nervous system may obscure associations between HRV and health markers typically found in healthy populations. For example, physical training improved spectral HRV in diabetics without cardiovascular neuropathy and with mild neuropathy [43]. However, in those with severe cardiovascular neuropathy, the physical activity intervention did not demonstrate any benefit [43]. Further, vagally mediated heart rate recovery in patients with chronic HF is blunted after exercise in comparison to healthy individuals [44], which is likely due to changes in autonomic function caused by HF. In HF, compensatory countermeasures, such as increased sympathetic nervous system activity, are chronically activated to maintain cardiac function [45]. After chronic overactivation of these systems, functionality becomes impaired and the typical association found between HRV and physical activity or physical fitness is likely obscured.

Numerous mechanisms between CVD and depression have been proposed. In a review by Joyst, Whellan, and O'Connor [46], factors such as noncompliance with medical regimens, clustering of risk factors (e.g., smoking, obesity), inflammation, stress, and decreased HRV have all been implicated in the association between CVD and depression. Additionally, although antidepressant medication has been hypothesized as mediating the effect, only tricyclic medication significantly impacted HRV in a meta-analysis [47]. Although depression has largely been considered an independent risk factor for CVD and mortality [48], little research has elucidated the

direction of associations. In a large longitudinal cohort study, Jandackova, Britton, Malik, and Steptoe [18] concluded that in those without depressive symptoms, lower heart rate and HRV predicted future incident depressive symptoms. Additional research replicating and better clarifying the direction of the association between HRV and depressive symptoms is needed.

Findings in this sample of HF patients are novel and contradictory to those found in other cardiac samples. No studies to date have examined the impact of physical fitness on the association between depressive symptoms and HRV in HF patients. Given the high prevalence of depression and suppressed HRV characteristics of HF, interventions addressing these predictors of poor outcomes may be warranted. As clinically significant depression is estimated to occur in 21.6% of HF patients [49], depression may be a potential target for treatment to enhance autonomic function. Additionally, depressive symptoms predict higher rates of cardiac events and mortality [50] and short-term declines in health status [51] in HF patients.

Limitations regarding this study are notable. As previously mentioned, compromised autonomic nervous systems of HF patients may provide less reliable HRV measures. Interestingly, HRV was not negatively correlated with age in this sample, which is uncharacteristic of the variable [52] and raises concerns about the validity of the measure. Further, respiration was not controlled for and can impact short-term recordings of HRV [53], which were used in this sample. Listwise deletion was used to exclude those with missing HRV data, which limits interpretability of findings to only those patients from which adequate ECG recordings can be obtained. Next, physical fitness scores were restricted in range, with approximately half of the sample demonstrating impaired or poor fitness, which could be problematic in analyses. Other factors may also have affected physical fitness, such as medication use, implantable medical devices, or differences in ejection fraction among patients. Additionally, this study used cross-sectional data which limits conclusions about causality. Our sample was primarily Caucasian, comprised HF patients, and included a relatively small sample of clinical cardiac patients; thus, findings may not generalize to different populations. Future studies should consider potential mechanisms and confounds such as nutritional habits.

Consistent with the literature on depression and autonomic function in cardiac samples, HRV was negatively associated with depressive symptoms in this sample of HF patients. However, this association was not attenuated when including physical fitness in a regression model. In HF patients, compromised autonomic function may obscure important associations with HRV. However, it is important to consider intervention implications

with HF patients. During the course of interventions that target secondary prevention, such as exercise-based cardiac rehabilitation, devoting greater attention to screening and, if necessary, treatment of depression may be both psychologically and physiologically more beneficial to HF patients.

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#### Compliance with Ethical Standards

**Authors' Statement of Conflict of Interest and Adherence to Ethical Standards** Authors Fawn A. Walter, Emily Gathright, Joseph D. Redle, John Gunstad, and Joel W. Hughes declare that they have no conflict of interest.

**Author contributions** FAW conceived of and designed analysis, interpreted data, drafted and revised for intellectual content, final approval of version to be published. EG provided statistical consultation and contributed to revisions. JR investigator and contributed to design of parent study; reviewed article for content. JG investigator and contributed to design of parent study, reviewed article for content. JWH primary investigator of parent study, substantially contributed to conception and design of study, revised it critically for intellectual content.

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## Background

Cardiovascular diseases (CVDs) and depression are among the leading causes of the global disease burden [1]. CVDs are the most common cause of death accounting for 17.9 million deaths globally, in 2015 [2]. Depression affects over 300 million people around the world [3], and is expected to become the main cause of disability globally, in 2030 [4]. Similarly, in 2010, anxiety affected approximately 272 million people, worldwide [5].

There is a high prevalence of mental disorders, particularly depression and anxiety, in CVD patients [6]. The bi-directional link between CVDs and these mental disorders has been extensively documented in literature [7–9]. Approximately, 15–30% of patients with CVD suffer from depressive disorders [10–14]. These rates of depression are two to three times higher than in the general population [15]. Moreover, depression and anxiety have been found to worsen prognosis and quality of life in patients with coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), unstable angina, and coronary artery bypass grafting (CABG) [16–22]. CABG is defined as a surgical procedure that is performed to treat people who have severe coronary heart disease, which improves blood flow to the heart [23]. They were also found to be the biggest driver of health care costs in coronary heart disease (CHD) patients [24].

Mental health problems have a direct physiological effect on the course of cardiac disease and their adverse effect may be mediated by non-compliance to lifestyle interventions, treatment and medication [25, 26]. Furthermore, these mental disorders add to the burden of managing CVD, from a perspective of treatment complexity and emotional distress. This problem is further aggravated by the high rate of additional co-morbidities such as diabetes, hypertension and obesity [27].

The American Heart Association (AHA) has recommended routine depression screening in cardiac patients [26]. However, health systems have not yet adequately responded and less than 15% of cardiac patients are being diagnosed and treated for depression [28]. Integrating mental health into cardiac treatment is of particular relevance in low-middle-income countries (LMICs), where the burden of depression and anxiety is often high and aggravated by adverse life and political conditions. Similarly, mental health problems are stigmatized in many of these non-western cultures [29]. Little is known on the prevalence of depression and anxiety among cardiac patients in LMICs [30]. This also applies to Palestine, where mental disorders commonly are not recognized, diagnosed or treated, despite the increase in their prevalence [31]. Unaddressed mental care needs may be an important barrier to the successful management of cardiac patients in Palestine, where CVD remains the leading cause of death [32].

Mental health problems have not been studied in cardiac patients in the Palestinian population. Therefore, the aim of the current study was to determine the proportion of patients with depression and anxiety symptoms admitted with a cardiac diagnosis, to one of the four main hospitals in Nablus, Palestine. To guide physicians in effective mental health screening in the future, we also identified socio-demographic, clinical, psychosocial, and lifestyle factors associated with a high risk of depression and anxiety symptoms.

## Methods

### Study design and population

This cross-sectional hospital-based study was conducted on patients consecutively admitted to the cardiology and cardiac surgery departments of An-Najah National University Hospital, Arab-Specialized Hospital, Watani Hospital and Nablus Specialized Hospital in the Northern West Bank city of Nablus, Palestine. Patients were eligible for the study if they were between 30 and 80 years of age and had an existing or newly confirmed cardiac diagnosis warranting hospitalization during the period between March and November 2017. In the present study, cardiac diagnoses considered included CAD, ST elevation or non-ST elevation MI, angina, HF, cardiac arrhythmia, valve disease or any other cardiac disease. Diagnoses were confirmed using hospital medical charts. Patients were excluded if they had a normal cardiac catheterization (CATH), an acute or past stroke, end-stage kidney disease (including dialysis patients), peripheral vascular disease, major co-morbidities affecting mental health (alcohol abuse, drug abuse), neurological disorders (dementia, Alzheimer's disease, epilepsy, Parkinson's disease), cognitive impairment, a severe clinically diagnosed psychiatric condition or any other condition affecting the quality of their responses.

Eligible patients were recruited for in-person interviews by trained medical research assistants. Patients were identified using hospital registries and medical records. Interviews were conducted while patients were awaiting treatment (after CATH) or after their treatment, within 1 week of their admission to the hospital. Eligible patients were informed about the study objectives and benefits and written informed consent was obtained from those who agreed to participate. The study was approved by the Ethics Committee of Nordwest- und Zentral Schweiz (EKNZ) in Basel, Switzerland, and by the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine.

### Study assessments and measures

Data was collected using a structured questionnaire consisting of two parts (Tables 1 and 2; see Additional file 1 for more detailed description). The first part included

detailed socio-demographic and clinical information obtained from patients' administrative and medical charts.

The second part was administered during a private interview and consisted of a sequence of screening instruments. These validated tools have demonstrated to be suitable for clinical populations to assess for depression and anxiety symptoms, QoL, post-traumatic stress disorder (PTSD), social support, resilience, self-esteem, somatic symptoms and lifestyle behaviors. The questionnaire, including the instruments, was translated from English to Arabic and back-translated from Arabic to English by two bilingual experts.

### Statistical analyses

The primary endpoints in the present study were depression and anxiety. Descriptive statistics for stress as an endpoint are presented in an Additional file 2: Table S2, with no further description. The four predictor blocks investigated for association with depression and anxiety were socio-demographic, clinical, psychosocial and lifestyle factors (Table 1). Endpoints and predictors were described as means and standard deviations (SD) for quantitative variables and as absolute values and percentages for categorical variables. Differences in predictor variables according to presence or absence of depression and anxiety symptoms were described using chi-squared test and the Wilcoxon rank sum test, as appropriate. Fisher's exact test was used for results presenting a frequency below five. Multivariate ordered logistic regression analyses were performed to examine the independent association between predictor variables and depression or anxiety symptoms. All variables were entered in each of the models at once. Results are presented in separate models for depression and anxiety and are expressed as odds ratio (OR) and 95% confidence intervals (95% CI). The cut-offs for the respective outcome variables were normal, mild/moderate, and severe/very severe according to standardized cut-offs. Correlations between the outcome variables and other instruments used in the study were assessed using Spearman's rank correlation coefficient. Cronbach alpha was used to assess the internal consistency of the different scales. Statistical significance

was defined as a two-sided *p*-value <0.05. All data was analyzed using the STATA Data Analysis and Statistical Software, version 14.

## Results

In total, 1092 patients were eligible and approached for an interview. Among the 1053 (96%) patients which agreed to participate in the study, 1022 patients with complete outcome and predictor information were used in the analysis.

### Characteristics of study population

Characteristics of the participants are presented in Table 3.

#### Socio-demographic factors

Among the 1022 patients, 73.4% were males. The mean age of patients was  $58.9 \pm 10.1$  years (range 30–80 years). The majority of participants were married (90.6%), 37% were unemployed, and 58.7% did not have a high school diploma. Most of the study population lived in cities (46.4%) or villages (46.3%), while 7.3% resided in refugee camps.

#### Clinical factors

The primary diagnoses among the sample were MI (39.7%), CAD (32.7%), angina (15.9%) and other diagnoses (11.7%), including mitral or aortic valve stenosis, valve regurgitation, heart block and others. Among the category of other diagnoses, 29 (2.8%) patients had heart failure. Over 60% of participants had a previous cardiac diagnosis and had been diagnosed with a cardiac disease for 1 year or less. About half of participants underwent a CATH with a stent (52.2%), while others underwent a CATH with a CABG (23.5%), or some kind of other procedure (24.3%), which was not yet performed at the time of the interview. Forty one percent of participants reported having two or more co-morbidities (mainly diabetes and hypertension) and 72.2% were on three or more medications. In addition, more than half of the participants' reported a family history of CVD. Approximately 37% of participating patients exhibited high somatic symptoms

**Table 1** Predictor blocks used in bivariate and ordered logistic regression analyses

Block	Variable
1 Socio-demographic factors	Age, gender, marital status, residence, education level, occupation
2 Clinical factors	Current diagnosis, previous cardiac diagnoses, years with cardiac disease, cardiac treatment (at admission), co-morbidities, medications, somatic symptoms (PHQ-15), family history of CVD, QoL (SF-12-PCS)
3 Psychosocial factors	PTSD (PTSD-PCL-S), social support (ESSI), resilience (RS-14), self-esteem, QoL (SF-12-MCS)
4 Lifestyle factors	Smoking status, currently on diet, fat consumption, vegetable and fruit consumption, alcohol use, physical activity, BMI

Note. CVD Cardiovascular disease, QoL Quality of life, PHQ-15 Patient health questionnaire-15, PCS Physical component summary, PTSD Post-traumatic stress disorder, PCL-S Post-traumatic stress disorder checklist, ESSI ENRICHED Social support instrument, RS-14 Resilience scale-14, MCS Mental component summary, BMI Body mass index

**Table 2** Study Instruments (see Additional file 1 for further descriptions)

Instrument	Description
Outcomes - assessment of depression, anxiety and stress	
Cardiac Depression (CDS)	The primary outcome of the study was measured using the Cardiac Depression Scale (CDS) by Hare et al., a disease-specific, 26-item questionnaire used to measure depression in patients with CVDs. CDS scores range from 26 to 182, and items are scored on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree) [60]. The CDS can be used as a continuous measure, where higher scores indicate higher depressive symptoms or as an ordinal indicator of possible depression using cut-off points previously used in literature. In this study, the presence of mild-to-moderate depression was defined as a CDS score of 90–100 and the presence of severe depression as a score >100. Scores below 90 indicated no-to-minimal depression [63].
Depression, anxiety, stress (DASS-42)	Depression (DASS-depression), anxiety (DASS-anxiety) and stress (DASS-stress) were measured using the Depression Anxiety Stress Scale-42 (DASS-42) by Lovibond & Lovibond, a 42-item questionnaire consisting of three subscales, each containing 14 items scored on a four-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much), measuring the extent to which each item was experienced over the past week. The scores are classified as: depression 0–9 (normal), 10–20 (mild-moderate), > 21 (severe-very severe); anxiety 0–7 (normal), 8–14 (mild-moderate), > 15 (severe-very severe); stress 0–14 (normal); 15–25 (mild-moderate), > 26 (severe-very severe) [64].
Predictors – correlates of depression and anxiety	
Somatic Symptoms (PHQ-15)	The Patient Health Questionnaire (PHQ-15) is a 15-item somatic symptom scale derived from the full Patient-Health-Questionnaire to measure the severity of somatization in patients [65].
Quality of life (SF-12-PCS; SF-12-MCS)	Quality of life was assessed using the 12-item Short-Form Health Survey (SF-12), which is a generic measure of overall health status. The SF-12 is comprised of two components, the Mental Component Summary (MCS) score and the Physical Component Summary (PCS) score [66].
Post-traumatic stress disorder (PTSD-PCL-S)	The Post-Traumatic Stress Disorder Checklist (PTSD-PCL-S) is a 17-item scale used to assess PTSD symptoms based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. The PTSD-PCL-S is used to link symptom endorsements to a specific stressful or traumatic event or experience [67].
Social Support (ESSI)	The ENRICHED (Enhancing Recovery in Coronary Heart) Social Support Instrument (ESSI) is a seven-item scale comprised from the Medical Outcomes Survey (MOS). It assesses four components of social support including emotional, instrumental, informational and appraisal [68, 69].
Self-esteem (SE)	The Single-Item Self-Esteem Scale is a one-item scale developed as an alternative of the Rosenberg Self-Esteem scale [70].
Resilience (RS-14)	Resilience Scale (RS-14) is a 14-item questionnaire that assesses individual resilience in a general population [71].

on the PHQ-15. The mean score of the participants on the SF-12- PCS score was  $37.6 \pm 12.4$ .

#### Psychosocial factors

Forty Percent of patients reported having PTSD symptoms on the PTSD-PCL-S. Social support was generally high (64%) among participants, according to the ESSI. Almost half of the participants presented with moderate to moderately-high resilience. The mean score for self-esteem was  $5.8 \pm 1.4$ , while the mean score for the SF-12-MCS was  $39.7 \pm 13.2$ .

#### Lifestyle factors

Almost half of the participants were current smokers while 35.6% had never smoked before. The vast majority of participants (83.4%) reported not being on a diet, 47% low fat consumption, and 55.5% high vegetable and fruit consumption. The reported alcohol consumption was very low with 95% of participants not consuming any alcohol. Almost half of the patients reported no-to-minimal daily physical activity. Eighty percent of patients were either overweight or obese.

#### Proportion of patients with depressive and anxiety symptoms at different severity levels

Table 4 shows the proportion of patients with depression (CDS), depression (DASS-depression), anxiety (DASS-anxiety) and stress (DASS-stress) symptoms at different severity levels. Cutoffs for the levels of CDS and DASS subscales are also presented in Table 4. Based on our findings, the  $\text{mean} \pm \text{SD}$  depression score on the CDS was  $101.3 \pm 15.6$  and the overall proportion of patients with depression was 78.7%. According to the recommended cutoffs for the CDS, 21.3, 25.2 and 53.5% of the sample had no, mild-to-moderate and severe-to-very severe depression symptoms, respectively. The means  $\pm$  SDs on the DASS-42 were  $9.4 \pm 8.6$ ,  $9.4 \pm 6.8$  and  $15.2 \pm 9$  for depression, anxiety, and stress, respectively. It was found that the overall proportion was 52.9, 53.1 and 37.4% for the presence of depressive, anxiety and stress symptoms according to the DASS-42. Based on recommended cutoffs, 47.1, 33.4 and 19.5% of patients reported normal, mild-to-moderate and severe-to-very severe depressive symptoms (DASS-depression). In addition, 46.9% patients did not report any anxiety,

**Table 3** Socio-demographic, clinical, psychosocial and lifestyle characteristics of study population, (n = 1022)

Variable	n(%)
Socio-demographic factors	
Age, mean (SD)	58.9 ± 10.1
Gender	
Female	272 (26.6)
Male	750 (73.4)
Marital status	
Married	926 (90.6)
Not married	96 (9.4)
Residence	
City	474 (46.4)
Village	473 (46.3)
Camp	75 (7.3)
Education degree	
No HS diploma	600 (58.7)
HS diploma	167 (16.3)
College degree	255 (25.0)
Occupation	
Professional	209 (20.5)
Non-professional	307 (30.0)
Unemployed	378 (37.0)
Retired	81 (7.9)
House wife	47 (4.6)
Clinical factors	
Cardiac diagnosis	
CAD	334 (32.7)
MI	406 (39.7)
Angina	162 (15.9)
Other	120 (11.7)
Previous cardiac diagnosis	
Yes	690 (67.5)
No	332 (32.5)
Years with cardiac disease	
≤ 1 year	628 (61.5)
2–9 years	255 (24.9)
≥ 10 years	139 (13.6)
Cardiac treatment (at admission)	
CATH/stent	534 (52.2)
CATH/CABG	240 (23.5)
CATH/other & unknown	248 (24.3)
Co-morbidities	
None	299 (29.3)
One	303 (29.6)
Two or more	420 (41.1)

**Table 3** Socio-demographic, clinical, psychosocial and lifestyle characteristics of study population, (n = 1022) (Continued)

Variable	n(%)
Medications	
None	132 (12.9)
1–2	152 (14.9)
3–4	738 (72.2)
Somatic symptoms (PHQ-15)	
Minimal	91 (8.9)
Low	241 (23.6)
Medium	314 (30.7)
High	376 (36.8)
Family history	
Yes	614 (60.1)
No	408 (39.9)
QoL, (SF-12-PCS score), mean (SD)	
	37.6 ± 12.4
Psychosocial factors	
PTSD (PTSD-PCL-S)	
Minimal	611 (59.7)
Some	95 (9.3)
Moderate	253 (24.8)
High	63 (6.2)
Social support (ESSI)	
Low	364 (35.6)
High	658 (64.4)
Resilience (RS)	
Very low	92 (9.0)
Low	103 (10.1)
Low-end	204 (20.0)
Moderate	257 (25.1)
Moderately-high	274 (26.8)
High	92 (9.0)
Self-esteem (SE) score, mean (SD)	
	5.8 ± 1.4
QoL, (SF-12-MCS score), mean (SD)	
	39.7 ± 13.2
Lifestyle factors	
Smoking status	
Never	364 (35.6)
Former	170 (16.6)
Current	488 (47.8)
Currently on diet	
Yes	170 (16.6)
No	852 (83.4)
Fat consumption	
Low	480 (47.0)

**Table 3** Socio-demographic, clinical, psychosocial and lifestyle characteristics of study population, (n = 1022) (Continued)

Variable	n(%)
Medium	323 (31.6)
High	219 (21.4)
Vegetable & fruit consumption	
Low	102 (10.0)
Medium	353 (34.5)
High	567 (55.5)
Alcohol use, (n = 1019)	
Yes	49 (4.8)
No	973 (95.2)
Physical activity	
None	337 (33.0)
Not daily	189 (18.5)
Daily	496 (48.5)

Note. HS High school, MI Myocardial infarction, CAD Coronary artery disease, CATH Catheterization, CABG Coronary artery bypass graft, CVD Cardiovascular disease, PHQ-15 Patient health questionnaire-15, PCS Physical component summary, QoL Quality of life, SD Standard deviation, PTSD Post-traumatic stress disorder, PTSD-PCL-S Post-traumatic stress disorder checklist, ESSI ENRICHED social support instrument, RS-14 Resilience scale-14, MCS Mental component summary, BMI Body mass index

while 33.9% reported mild-to-moderate anxiety and 19.2% reported severe-to-very severe anxiety symptoms. According to the stress scale, 62.6% reported having no stress, 30% reported having mild-moderate stress symptoms and 7.4% severe-very severe stress symptoms. Patients that had mild-moderate and severe-very severe

symptoms of depression or anxiety according to the DASS-42 were more likely to have severe depressive symptoms on the CDS. Nevertheless, 8 (4.0%) and 9 (4.6%) patients without any signs of depressive symptoms on the CDS, showed symptoms of depression and anxiety, respectively, on the DASS-42.

#### Unadjusted correlations between continuous scores of the scales used in study

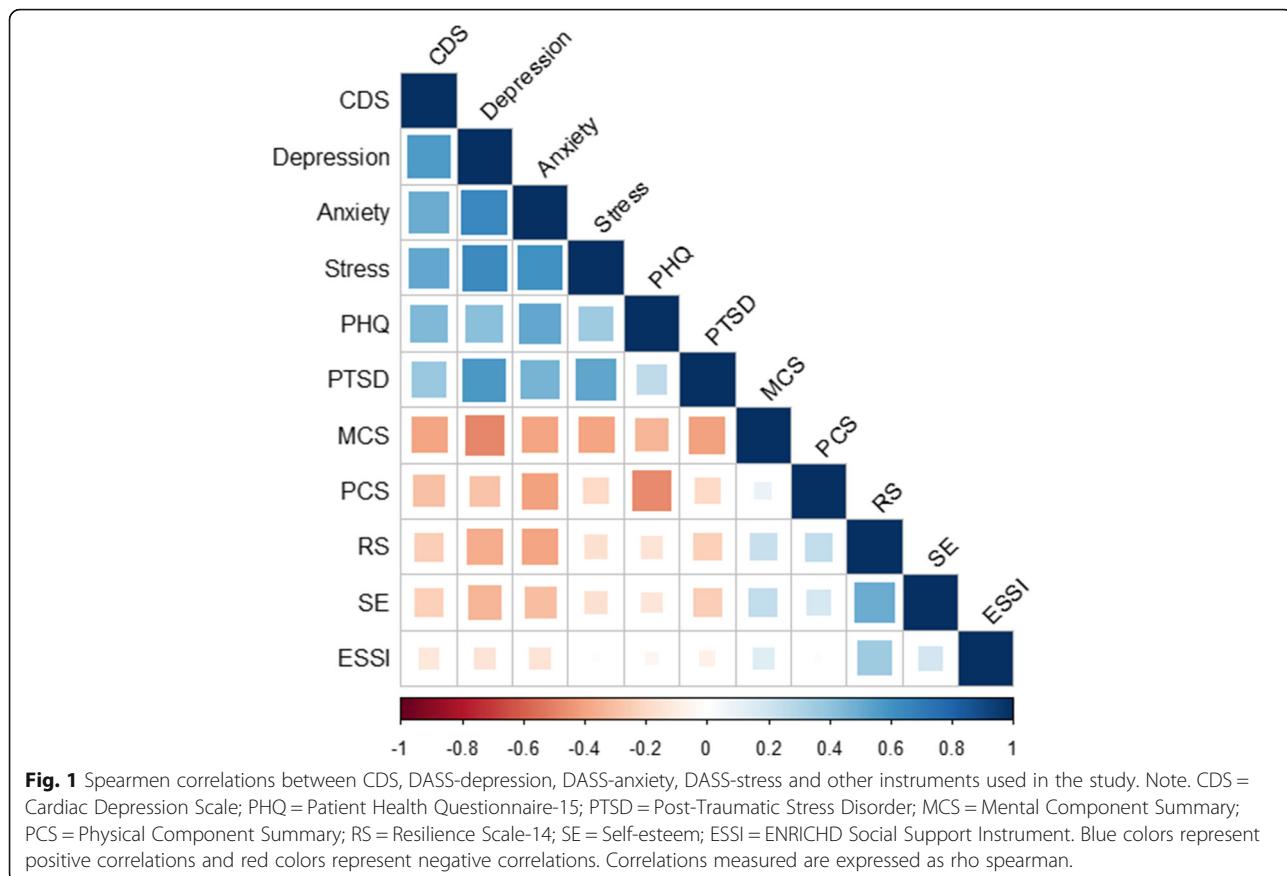
Spearman correlation coefficients were calculated between the CDS and other instruments used in the study (see Fig. 1). The correlation of the CDS with the DASS-depression was =0.57 ( $p < 0.001$ ), with DASS-stress =0.51 ( $p < 0.001$ ), and with DASS-anxiety =0.50 ( $p < 0.001$ ). The correlations between the DASS subscales were as follows: DASS-depression and DASS-anxiety (0.65,  $p < 0.001$ ); DASS-depression and DASS-stress (0.63,  $p < 0.001$ ); DASS-anxiety and DASS-stress (0.61,  $p < 0.001$ ). CDS was positively correlated with the PHQ-15 (0.44,  $p < .001$ ) and the PTSD-PCL-S (0.37,  $p < .001$ ) and the DASS-depression was also positively correlated with the PTSD-PCL-S (0.57,  $p < .001$ ).

The above cluster of positively associated factors were weakly correlated to the physical and mental QoL components of the SF-12, social support, resilience, and self-esteem, which were strongly correlated among each other. Specifically, weak correlations were observed between CDS and the SF-12-MCS ( $-0.39$ ,  $p < 0.001$ ), SF-12-PCS ( $-0.29$ ,  $p < 0.001$ ), ESSI ( $-0.12$   $p < 0.001$ ), RS-14 ( $-0.24$ ,  $p < 0.001$ ) and with the self-esteem scale ( $-0.23$ ,  $p < 0.001$ ).

**Table 4** Proportion of patients with CDS-depression, DASS-depression, DASS-anxiety, DASS-stress at different severity levels (n = 1022)

	Depression, anxiety, stress according to CDS levels			Percentage above normal level
	Normal n (%)	Mild- Moderate n (%)	Severe-very severe n (%)	
CDS	CDS < 90 218 (21.3)	CDS 90–100 257 (25.2)	CDS > 100 547 (53.5)	78.7
DASS-depression (D $\geq 10$ )	481 (47.1)	341 (33.4)	200 (19.5)	52.9
Normal (0–9)	166 (34.5)	164 (35.1)	151 (31.4)	
Mild/moderate (10–20)	44 (12.9)	82 (24.1)	215 (63.1)	
Severe/very severe (21–42)	8 (4.0)	11 (5.5)	181 (90.5)	
DASS-anxiety, (A $\geq 7$ )	479 (46.9)	347 (33.9)	196 (19.2)	53.1
Normal (0–6)	152 (31.7)	164 (34.2)	163 (34.0)	
Mild/moderate (7–14)	57 (16.4)	77 (22.2)	213 (61.4)	
Severe/very severe (15–42)	9 (4.6)	16 (8.2)	171 (87.2)	
DASS-stress, (S $\geq 15$ )	640 (62.6)	307 (30.0)	75 (7.4)	37.4
Normal (0–14)	178 (27.8)	206 (32.2)	256 (40.0)	
Mild/moderate (15–25)	36 (11.7)	44 (14.3)	227 (73.9)	
Severe/very severe (26–42)	4 (5.3)	7 (9.3)	64 (85.3)	

Note. CDS Cardiac depression scale, DASS Depression, anxiety, stress scale



### Association between socio-demographic, clinical, psychosocial, lifestyle factors and depressive and anxiety symptoms

The bivariate distribution of socio-demographic, clinical, psychological, and lifestyle characteristics according to the presence or absence of depression symptoms (CDS), anxiety symptoms (DASS-anxiety) and stress symptoms (DASS-stress) is presented in Additional file 3: Table S1 (depression (CDS) and anxiety) and Additional file 2: Table S2 (stress). Briefly, with regard to socio-demographic factors, bivariate analysis revealed depressive and anxiety symptoms were more frequent among females than males (depression: 84.9% vs. 76.4%,  $p = 0.003$ ; anxiety: 72.4% vs. 55.6%,  $p < 0.001$ ) and among those with lower educational level (depression: 81.0% [no high school diploma] vs. 78.0% [high school diploma] and 71.1% [college degree],  $p = 0.02$ ; anxiety: 63.2% [no high school diploma] vs. 59.8% (high school diploma) and 52.8% (college degree),  $p < 0.05$ ). Both, depressive and anxiety symptoms were most prevalent among those unemployed and housewives (depression:  $p < 0.001$ ; anxiety:  $p < 0.001$ ).

Multivariable ordered logistic regression was performed to determine the independent association of factors in the four predictor blocks with a) depressive symptoms, categorized as no depressive symptoms, moderate depressive

symptoms, and severe depressive symptoms according to the CDS and b) anxiety symptoms, categorized as minimal anxiety symptoms, mild-moderate anxiety symptoms, and severe-severe anxiety symptoms according to the DASS-anxiety subscale. The results for the four blocks of variables are presented in Table 5.

Overall, most of the psychosocial factors were consistently associated with both, depression and anxiety. Participants with depression or anxiety were more likely to exhibit at least some symptoms of PTSD. Odds ratios tended to be higher for anxiety than for depression (moderate symptoms vs. minimal symptoms:  $OR_{\text{depression}} 1.87$  (95% CI 1.29–2.71) vs.  $OR_{\text{anxiety}} 3.01$  (95% CI 2.12–4.27)). Patients with depression or anxiety had a lower score for the mental component of QoL (SF-12-MCS) [ $OR_{\text{depression}} 0.96$  (95% CI 0.95–0.97);  $OR_{\text{anxiety}} 0.98$  (95% CI 0.97–0.99)]. High resilience and high social support were inversely associated with depression and anxiety [high vs. low social support:  $OR_{\text{depression}} 0.71$  (95% CI 0.52–0.97);  $OR_{\text{anxiety}} 0.74$  (95% CI 0.54–1.00)]. The inverse association with resilience tended to be stronger in the presence of anxiety [high vs. very low resilience:  $OR_{\text{depression}} 0.42$  (95% CI 0.18–0.94);  $OR_{\text{anxiety}} 0.22$  (95% CI 0.11–0.48)].

In addition to psychosocial factors, the physical component of QoL (SF-12-PCS) and somatic symptoms

**Table 5** Factors associated with DEPRESSION and ANXIETY in multivariate ordered logistic regression

Variable	Depression (CDS)			Anxiety (DASS-anxiety)		
	OR	95% CI	P value	OR	95% CI	P value
<b>Socio-demographic factors</b>						
Age, mean (SD)	0.99	(0.98–1.00)	0.393	<b>0.96</b>	<b>(0.95–0.99)</b>	< 0.001
Gender						
Female	(reference)			(reference)		
Male	0.83	(0.51–1.36)	0.469	0.68	(0.43–1.10)	0.117
Marital status						
Married	(reference)			(reference)		
Not married	<b>0.38</b>	<b>(0.22–0.65)</b>	<b>0.001</b>	1.28	(0.76–2.13)	0.350
Residence						
City	(reference)			(reference)		
Village	1.22	(0.91–1.64)	0.191	0.74	(0.54–1.00)	0.054
Camp	1.35	(0.76–2.40)	0.308	0.56	(0.31–1.01)	0.054
Education degree						
No HS diploma	(reference)			(reference)		
HS diploma	1.15	(0.82–1.62)	0.421	0.93	(0.65–1.31)	0.666
College degree	1.19	(0.76–1.87)	0.449	1.09	(0.68–1.76)	0.715
Occupation						
Professional	(reference)			(reference)		
Non-professional	0.85	(0.55–1.31)	0.472	1.15	(0.73–1.81)	0.544
Unemployed	1.12	(0.67–1.88)	0.662	0.89	(0.54–1.48)	0.660
Retired	0.71	(0.38–1.33)	0.289	1.44	(0.75–2.73)	0.269
House wife	<b>0.33</b>	<b>(0.14–0.80)</b>	<b>0.014</b>	0.65	(0.27–1.56)	0.335
<b>Clinical Factors</b>						
Cardiac diagnosis						
CAD	0.89	(0.63–1.25)	0.508	0.75	(0.53–1.07)	0.111
MI	(reference)			(reference)		
Angina	1.26	(0.83–1.92)	0.271	0.54	(0.35–0.86)	0.009
Other	0.82	(0.49–1.37)	0.440	1.23	(0.76–1.99)	0.407
Previous cardiac diagnosis						
Yes	<b>0.67</b>	<b>(0.47–0.96)</b>	<b>0.028</b>	<b>1.52</b>	<b>(1.05–2.21)</b>	<b>0.026</b>
No	(reference)			(reference)		
Years with cardiac disease						
≤ 1 year	(reference)			(reference)		
2–9 years	<b>1.46</b>	<b>(1.00–2.13)</b>	<b>0.048</b>	1.10	(0.76–1.59)	0.663
≥ 10 years	<b>1.71</b>	<b>(1.06–2.75)</b>	<b>0.028</b>	0.95	(0.60–1.50)	0.832
Cardiac treatment (at admission)						
CATH/stent	(reference)			(reference)		
CATH/CABG	1.42	(0.98–2.04)	0.065	0.89	(0.62–1.29)	0.558
CATH/other & unknown	1.34	(0.95–1.89)	0.097	<b>1.44</b>	<b>(1.02–2.04)</b>	<b>0.036</b>
Co-morbidities						
None	(reference)			(reference)		
1	0.93	(0.64–1.34)	0.695	0.96	(0.65–1.43)	0.860
2+	1.39	(0.94–2.04)	0.096	1.36	(0.92–2.01)	0.127

**Table 5** Factors associated with DEPRESSION and ANXIETY in multivariate ordered logistic regression (Continued)

Variable	Depression (CDS)			Anxiety (DASS-anxiety)		
	OR	95% CI	P value	OR	95% CI	P value
<b>Medications</b>						
None	(reference)			(reference)		
1–2	1.33	(0.78–2.29)	0.293	1.20	(0.68–2.10)	0.521
3–4	1.19	(0.74–1.92)	0.470	1.31	(0.79–2.18)	0.299
<b>Somatic symptoms (PHQ-15)</b>						
Minimal	(reference)			(reference)		
Low	1.18	(0.72–1.94)	0.506	1.41	(0.74–2.72)	0.296
Medium	<b>1.86</b>	<b>(1.12–3.08)</b>	<b>0.015</b>	<b>3.35</b>	<b>(1.76–6.35)</b>	<b>&lt; 0.001</b>
High	<b>3.00</b>	<b>(1.73–5.18)</b>	<b>&lt; 0.001</b>	<b>7.64</b>	<b>(3.96–14.78)</b>	<b>&lt; 0.001</b>
<b>Family history</b>						
Yes	1.03	(0.77–1.38)	0.824	0.76	(0.57–1.03)	0.075
No	(reference)			(reference)		
QoL, (SF-12-PCS score)	<b>0.98</b>	<b>(0.97–1.00)</b>	<b>0.015</b>	<b>0.97</b>	<b>(0.96–0.99)</b>	<b>&lt; 0.001</b>
<b>Psychosocial factors</b>						
PTSD (PTSD-PCL-S)						
Minimal	(reference)			(reference)		
Some	1.32	(0.83–2.10)	0.247	<b>2.34</b>	<b>(1.47–3.71)</b>	<b>&lt; 0.001</b>
Moderate	<b>1.87</b>	<b>(1.29–2.71)</b>	<b>0.001</b>	<b>3.01</b>	<b>(2.12–4.27)</b>	<b>&lt; 0.001</b>
High	1.28	(0.00)	0.974	<b>7.37</b>	<b>(3.89–14.0)</b>	<b>&lt; 0.001</b>
Social support (ESSI)						
Low	(reference)			(reference)		
High	<b>0.71</b>	<b>(0.52–0.97)</b>	<b>0.032</b>	<b>0.74</b>	<b>(0.54–1.00)</b>	<b>0.049</b>
Resilience (RS-14)						
Very low	(reference)			(reference)		
Low	1.05	(0.49–2.25)	0.896	0.76	(0.41–1.41)	0.381
Low-end	0.78	(0.39–1.56)	0.479	<b>0.43</b>	<b>(0.25–0.77)</b>	<b>0.004</b>
Moderate	0.60	(0.30–1.21)	0.154	<b>0.37</b>	<b>(0.20–0.66)</b>	<b>0.001</b>
Moderately-high	<b>0.48</b>	<b>(0.23–0.98)</b>	<b>0.044</b>	<b>0.19</b>	<b>(0.10–0.36)</b>	<b>&lt; 0.001</b>
High	<b>0.42</b>	<b>(0.18–0.94)</b>	<b>0.035</b>	<b>0.22</b>	<b>(0.11–0.48)</b>	<b>&lt; 0.001</b>
Self-esteem (SE) score	0.97	(0.85–1.10)	0.640	0.85	(0.76–0.96)	<b>0.007</b>
QoL(SF-12-MCS score)	<b>0.96</b>	<b>(0.95–0.97)</b>	<b>&lt; 0.001</b>	<b>0.98</b>	<b>(0.97–0.99)</b>	<b>&lt; 0.001</b>
<b>Lifestyle factors</b>						
Smoking status						
Never	(reference)			(reference)		
Former	<b>1.87</b>	<b>(1.17–2.97)</b>	<b>0.008</b>	0.71	(0.44–1.14)	0.154
Current	<b>1.61</b>	<b>(1.11–2.33)</b>	<b>0.013</b>	1.37	(0.93–2.02)	0.106
Currently on diet						
Yes	<b>0.59</b>	<b>(0.40–0.86)</b>	<b>0.007</b>	1.45	(0.98–2.13)	0.060
No	(reference)			(reference)		
Fat consumption						
Low	(reference)			(reference)		
Medium	0.73	(0.53–1.00)	0.054	1.09	(0.79–1.51)	0.583
High	0.79	(0.55–1.14)	0.206	1.28	(0.88–1.86)	0.187

**Table 5** Factors associated with DEPRESSION and ANXIETY in multivariate ordered logistic regression (Continued)

Variable	Depression (CDS)			Anxiety (DASS-anxiety)		
	OR	95% CI	P value	OR	95% CI	P value
Vegetable & fruit consumption						
Low	(reference)			(reference)		
Medium	0.83	(0.50–1.37)	0.466	<b>0.52</b>	<b>(0.31–0.86)</b>	<b>0.011</b>
High	0.73	(0.45–1.19)	0.207	0.80	(0.49–1.30)	0.375
Alcohol use						
Yes	1.31	(0.66–2.61)	0.439	1.19	(0.63–2.24)	0.591
No	(reference)			(reference)		
Physical activity						
None	(reference)			(reference)		
Not daily	<b>0.64</b>	<b>(0.42–0.98)</b>	<b>0.040</b>	<b>0.57</b>	<b>(0.37–0.87)</b>	<b>0.009</b>
Daily	<b>0.43</b>	<b>(0.30–0.60)</b>	<b>&lt; 0.001</b>	0.98	(0.70–1.38)	0.908
BMI						
Underweight	0.63	(0.05–7.7)	0.720	2.09	(0.22–19.9)	0.522
Normal weight	(reference)			(reference)		
Overweight	0.81	(0.55–1.18)	0.272	<b>0.61</b>	<b>(0.42–0.89)</b>	<b>0.010</b>
Obese	0.95	(0.63–1.43)	0.824	0.87	(0.59–1.29)	0.495

Note. Multivariate ordered logistic regression reported for socio-demographic, clinical, psychosocial and lifestyle factors associated with depression, CDS (not depressed; mild-moderate depression; severely-very severe depression) and DASS-anxiety (no anxiety, mild-moderate anxiety; severe-very severe anxiety). Analyses were performed in two separate models for depression and anxiety, mutually adjusting for all factors in the four predictor blocks in both models. Analyses are also adjusted for the hospital to which patients were admitted. OR Odds ratio, CI Confidence interval, SD Standard deviation, HS High school, MI Myocardial infarction, CAD Coronary artery disease, CATH Catheterization, CABG Coronary artery bypass graft, PHQ-15 Patient health questionnaire-15, PCS Physical component summary, PTSD Post-traumatic stress disorder, PTSD-PCL-S Post-traumatic stress disorder checklist, ESSI ENRICHD social support instrument, RS-14 Resilience scale-14, MCS Mental component summary, BMI Body mass index; P values in bold are significant at  $p < 0.05$

(PHQ-15) also showed consistent associations with both depression and anxiety [high vs. minimal somatic symptoms: OR<sub>depression</sub> 3.00 (95% CI 1.73–5.18); OR<sub>anxiety</sub> 7.64 (95% CI 3.96–14.78)]; [SF-12-PCS: OR<sub>depression</sub> 0.98 (95% CI 0.97–1.00); OR<sub>anxiety</sub> 0.97 (95% CI 0.96–0.99)]. Current smoking was associated with depression with the strongest odds ratio observed for depression and former smoking: OR 1.87 (95% CI 1.17–2.97). Finally, patients with depression and anxiety were more likely to be physically inactive compared to patients without the respective psychological problems.

A few factors exhibited associations with only one of the two mental health outcomes. For example, patients residing in villages or camps were less likely to show symptoms of anxiety compared to patients living in the city [(OR<sub>village</sub> 0.74 (0.54–1.00); OR<sub>camp</sub> 0.56 (0.31–1.01)]. Unemployment was positively associated with depression, but not anxiety. The presence of previous cardiac diagnoses was positively associated with anxiety, but inversely associated with depression [(OR<sub>depression</sub> 0.67 (95% 0.47–0.96); OR<sub>anxiety</sub> 1.52 (95% 1.05–2.21)]. Symptoms of depression were more frequent among patients with a cardiac diagnosis for more than 10 years compared to patients with a diagnosis for a year or less [years since first diagnosis  $\geq 10$  vs.  $\leq 1$  year OR 1.71 (95% 1.06–2.75)]. Patients who were diagnosed with angina

were more likely to have anxiety symptoms than those diagnosed with an MI. Underweight and obese participants were more likely to exhibit symptoms of anxiety than those of normal weight and overweight.

#### Reliability assessment (Cronbach's alpha) of the study instruments

Cronbach  $\alpha$  for the primary outcome variable, CDS was 0.86 and 0.92 (DASS-depression), 0.82 (DASS-anxiety), and 0.89 (DASS-stress) for the DASS subscales, respectively, indicating high consistency for the relevant psychometric scales. This indicates all scales exhibit acceptable internal consistency with little likelihood of item redundancy. Inter-item correlations between the 26 items of the CDS and the total CDS scores ranged from 0.08 to 0.58, and all correlations were statistically significant at the 0.01 level. Cronbach  $\alpha$  for the other scales used in the study was: 0.78 for PHQ-15, 0.86 for PTSD-PCL-S, 0.82 for ESSI and 0.88 for RS-14.

#### Discussion

In the present study, the observed rates of depressive and anxiety symptoms were high. Only 21% (CDS) and 46% (DASS-anxiety) of patients did not exhibit any symptoms of depression and anxiety, respectively. Our findings point to the need for integrating mental health care into cardiac

treatment. It is noteworthy that several factors found to be associated with depression and anxiety may serve as screening and possibly as intervention targets.

Rates of mental health problems reported in earlier studies for patients with different cardiac diagnoses and in different cultural and health system settings ranged from 14 to 73% [33–38] for depressive symptoms and 15 to 48% [33–37] for anxiety symptoms. These varying rates are explained in part by differences in sample sizes, the instruments and cutoffs used for classifying depression and anxiety and the type of cardiac disease targeted in studies.

Lower rates of depression than in the current study were observed in other settings including Norway (14%) [33], USA (15%) [39], Brazil (26.4%) [34] and Pakistan (14%) [36]. Similar among these studies, was the common psychiatric instruments used to assess for depression, all of which were not specific for cardiac populations. In contrast, a different study assessing depression using the CDS found a rate of 73.2% of severe depression in Iranian patients with acute coronary syndrome (ACS), a rate even higher than in this study [38].

Similar anxiety rates to the current study were observed in Iran (28.5%) [37] and Pakistan (18%) [36]. Interestingly, in another study conducted in Brazil, Meneghetti et al. found a very high prevalence of 48.4% for anxiety symptoms among ACS patients using the Hospital Anxiety and Depression Scale (HADS) [34]. A study in the USA also reported, 37% of patients with MI due to spontaneous coronary artery dissection screened for anxiety using the Generalized Anxiety Disorder 7-Item Scale (GAD-7) [35].

Mental health problems are generally high in the Palestinian population [31]. In the absence of a healthy control group the results of this study do not allow to conclude that depression and anxiety are more common in cardiac patients. However, cardiac patients are in particular need of treatment for depression and anxiety given that existing evidence points to their adverse effect on the course of heart disease. Furthermore, cardiac rehabilitation may be an efficient starting point to address mental health issues beyond the patient and to the extended family and social network. Given the shortage of mental health services available and the local economic instability in Palestine, the provision of additional services needs to be implemented in a cost-effective way. The identification of subgroups of cardiac patients at higher risk of depression and anxiety can guide screening and interventions.

In perspective of mental health screening among cardiac patients, focus should be given to females and less educated patients. The higher rates of depression and anxiety seen in these sub-groups were previously described in literature [34, 37, 40, 41]. Women seem to be more vulnerable to the trauma caused by cardiac events,

which leads to a deterioration in depression and anxiety symptoms [37]. As observed in some [34, 42, 43], but not all studies [37, 38, 44], the association between gender and social status may not be direct as suggested by the disappearance of gender and social status differences in the fully adjusted models [34, 37, 38, 42].

The presence of the following additional characteristics in cardiac patients should be a red flag for cardiologists to consider mental health care in cardiac practice: symptoms of PTSD, low levels of self-esteem, somatic symptoms, low QoL components, active smoking, physical inactivity, and longer disease duration. In contrast, a high level of resilience seems to reduce symptoms of psychological problems, as previously observed in patients with heart failure [45, 46]. Unlike findings reported previously, comorbidities were not consistently more common in the presence of mental health disorders [47]. Little is known about the association of PTSD symptoms with depression and anxiety in cardiac patients. A study conducted on 813 patients who received angiograms at a large U.S. Veterans Administration Medical Center found depression to be positively associated with PTSD, smoking and alcohol consumption [48]. Low MCS and PCS scores on the SF-12, smoking, and chest pain were recently identified as the strongest predictors of longitudinally sustained high levels of depression and anxiety in CHD patients [24].

Factors serving as targets for intervention include smoking, physical activity and social support. Smoking cessation interventions are crucial for cardiac rehabilitation, however in the presence of depression, results are less successful and interventions may need to be adapted [49]. Sedentary behavior, a risk factor for depression in the general population [50], was previously associated with depression according to the Beck Depression Inventory-II in patients hospitalized for ACS [51]. In a small non-randomized intervention study with heart failure patients, aerobic interval training decreased symptoms of depression over a period of 12-weeks [52]. In studies on breast cancer [53], promotion of physical activity may have the additional benefit of improving self-esteem, a factor associated with depression and anxiety in this study and a predictor of mortality in the general population [54]. In addition, according to previous studies [43, 55–58], the inverse association between high social support and low levels of anxiety and depression points to another important target for prevention as it is supported by firm evidence from previous studies. Poor social support among patients with ACS was observed in secondary analyses of a randomized trial to reduce the effectiveness of treatment with antidepressants [59]. The quality of social support plays an important role, as overprotective behaviors of partners can have an adverse effect [58]. Interestingly, in the current study marital status and social support were associated with presence of

depressive symptoms independently and in opposite directions.

The current study has several strengths. First, it utilized a broad set of validated instruments to identify depression and anxiety symptoms as well as associated factors. The overall validity of the CDS in this study was almost similar to levels originally reported by Hare and Davis [60]. The validity of the DASS-42 was satisfactory, in line with other findings of other studies, including those originally reported by Lovibond and Lovibond [61]. Furthermore, the CDS is the only psychometric scale suitable for the comparative depression assessment in heart disease patients, subjected to different interventions [60, 62]. This is evident in the present study, as depression rates were lower when assessed by the DASS-42. The CDS, also has excellent properties for the diagnosis of MDD, a score of  $\geq 95$  having a 97% sensitivity at 85% specificity (AUC 0.96) [62]. Second, the large sample size provided sufficient statistical power for testing independent associations. Third, the study subjects are well characterized, which allowed for addressing confounding. Fourth, the high participation rate decreased the likelihood of selection and participation bias. Finally, the findings of the study despite being hospital-based are likely generalizable to the entire cardiac patient population in the city of Nablus and surrounding cities of Palestine, considering the study sites provide cardiac care to a large percentage of cardiac patients in the area.

Nonetheless, the cross-sectional nature of the study does not enable us to make causal inferences. A long-term follow-up is foreseen to investigate the predictive effect of the study characteristics and predictors with regard to the course of depression, anxiety and heart disease. While the reliability of the previously validated instruments was confirmed in our study, the instruments have not been validated specifically for the context of cardiac patients in Palestine. Furthermore, some of the risk factors could only be captured broadly to avoid lengthy interviews. This likely caused some misclassification, as in the case of physical activity. Recall bias may have added to the misclassification of risks, given the retrospective nature of the interview. Also, the study was not sufficiently powered to investigate differences in the frequency of depression and anxiety as well as associated factors between relevant subgroups of clinical diagnoses, for example MI and HF. Finally, some patients were recruited at the time of admission and for the most part before receiving their intervention or diagnosis, and thus were under much pressure and stress. The level of depression and anxiety could have been overestimated and may decrease in part over the course of disease. The most appropriate time point to assess depression and anxiety from a prognostic perspective is unknown.

## Conclusions

The alarmingly high rate of depression and anxiety symptoms observed in cardiac patients in Palestine points to the need for integrating mental health care into cardiac rehabilitation. The prognostic value of depression and anxiety with regard to the course of heart disease, adherence to treatment and quality of life needs to be investigated. Treatment of psychological problems from the disease onset and onwards is crucial considering longer disease duration puts individuals at higher risk of being depressed. The expertise of social scientists and medical anthropologists is needed for identifying efficient means to overcome barriers related to the stigmatization of psychological disorders.

## Additional files

**Additional file 1:** Description of study instruments. (DOCX 39 kb)

**Additional file 2: Table S2.** Socio-demographic, clinical, psychosocial, lifestyle factors by STRESS status, ( $n = 1022$ ). (DOCX 24 kb)

**Additional file 3: Table S1.** Socio-demographic, clinical, psychosocial, lifestyle factors by DEPRESSION and ANXIETY status, ( $n = 1022$ ). (DOCX 24 kb)

## Abbreviations

ACS: Acute coronary syndrome; AHA: American Heart Association; BMI: Body mass index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CATH: Catheterization; CDS: Cardiac Depression Scale; CHD: Coronary heart disease; CI: Confidence interval; CVD: Cardiovascular disease; CVDs: Cardiovascular diseases; DASS-42: Depression Anxiety Stress Scale-42; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV; EKNZ: Ethics Committee of Nordwest-und Zentral Schweiz; ENRICHHD: Enhancing Recovery in Coronary Heart; ESSI: ENRICHHD Social Support Instrument; HF: Heart failure; HS: High school; IRB: Institutional Review Board; LMIC: Low-middle income countries; MCS: Mental Component Summary; MDD: Major depressive disorder; MI: Myocardial infarction; MOS: Medical Outcomes Survey; OR: Odds ratio; PCS: Physical Component Summary; PHQ-15: Patient Health Questionnaire-15; PTSD: Post-traumatic stress disorder; PTSD-PCL-S: Post-Traumatic Stress Disorder Checklist; QOL: Quality of life; RS-14: Resilience Scale-14; SD: Standard deviation; SE: Self-esteem; SF-12: The 12-item Short Form Health Survey

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

HA conducted data collection, analyzed and interpreted data, and wrote the manuscript. AAAlka supervised the data collection and the implementation of

the study in Palestine and edited the manuscript. AAlkh, AH, HO, JS, MT assisted in data collection. EZ and SHY contributed to designing the study. EZ and CS participated in planning the data analysis. CS supervised the statistical analysis. EZ, SHY, and CS contributed to the interpretation of the results. NPH designed the study, directed its implementation, data analysis and result interpretation. She edited all versions of the manuscript. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nordwest- und Zentral Schweiz (EKNZ) in Basel, Switzerland and by the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine. All patients enrolled in the study provided written informed consent.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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## Background

Currently, there is overwhelming evidence to show the health benefits of physical exercise [1]. The Global Burden of Disease study has classified sedentarism as the fifth leading cause of disease burden in Western Europe and as one of the main modifiable risk factors [2]. Yet, despite recommendations to promote exercise as a strategy capable of reducing the burden of chronic diseases, the frequency and intensity of physical activity in the population are rather disconcerting. Physical activity is currently ranked among the health determinants which exert most influence on morbidity and mortality. Moreover, exercise can partially reverse the effects of ageing in physiological functions and conserve functional reserve among older adults [3].

Depression is a common and disabling condition that affects over 120 million people worldwide [4] -at least one in five people during their lifetime- and has a significant impact on health status. While it is usually treated with antidepressants and/or psychological therapy, such treatments are not effective in all cases, and increasing attention has recently been given to some alternatives, and to aerobic exercise in particular [5].

Depressive disorders among the aged are a paradigm of geriatric care in terms of the importance of prevention, differences in pathogenesis, diagnostic and therapeutic complexity, associated high risk of failure, and severe impact on quality of life. Old age is the time of life when emotional fragility is accentuated. In addition to neurobiological changes in the brain, ageing inevitably entails an important loss over the years, not only in terms of individuals' emotions, but also in terms of their physical condition and social status. Depression is the most common psychological disorder among people over the age of 65 years and affects approximately 15% of this age group [6].

Recent years have witnessed a dramatic rise in the prescription of antidepressant drugs, which has greatly increased health spending. Over half of the total cost of depression corresponds to direct costs, with those generated by antidepressant drugs becoming increasingly relevant. These drugs have undesirable effects, especially among the older population, with their use often being continued indefinitely and unnecessarily. It would therefore seem reasonable to test new therapeutic modalities which, *a priori*, would have fewer adverse effects and, most likely, a lower impact on health expenditure.

Among the reasons why exercise could improve depression is the belief that, on the one hand, it could act as a distraction from negative thoughts and that, on the other, it is possibly important to master new skills. In addition, social contact could form part of this mechanism. Physical activity can have physiological effects, such

as bringing about changes in endorphin and monoamine levels, or decreases in the level of cortisol, the stress hormone, which may result in an improvement in patients' mood [7]. Recent studies suggest that exercise stimulates the growth of new nerve cells and releases proteins, e.g., brain-derived neurotrophic factor, to improve the survival of nerve cells [8, 9]. Even so, a significant degree of uncertainty surrounds the effectiveness of exercise on depression [10, 11], mainly due to methodological considerations [12].

It should be stressed that older adults tend to be underrepresented in clinical trials in which both pharmacological and non-pharmacological measures for depressive disorders are assessed. Accordingly, and because these disorders present with special characteristics and a wide degree of clinical polymorphism among the elderly (difficulty in recognising the symptoms of depression, frequent somatic complaints, etc.), it would be of interest to carry out a clinical trial exclusively on adults aged over 65 years. This population group often presents with co-morbidities and, as a result, may be undergoing poly-pharmacy treatments. It is therefore important to demonstrate the effectiveness of non-pharmacological measures, such as physical exercise, in the case of depressive disorders.

The National Institute for Clinical Excellence (NICE) [13] conducted a systematic review on the likelihood of remission, reduction of symptoms and adherence to treatment among patients with depression who did and those who did not do exercise, and the different treatments available (pharmacological, psychotherapeutic, etc.), including a total of 25 clinical trials. Although the data which compared physical activity to antidepressant drugs indicated that there were no significant differences, the confidence intervals used by the studies were very wide, with the result that there was insufficient evidence to arrive at a conclusion. Overall, however, the studies suggested a benefit for physical activity -and more specifically for group-based physical activity- in the treatment of minor depression and mild-to-moderate major depression. In addition, physical activity has the advantage of contributing other health benefits, beyond a simple improvement in symptoms of depression [14].

The Guideline of the Institute for Clinical Systems Improvement [15] considers that physical activity could be a useful tool for ameliorating the symptoms of major depression. Another systematic review [16], in which only three studies with patients suffering from major depression were included, reported that physical exercise programmes significantly reduced the symptoms of depression, though the conclusions were limited by the heterogeneity and methodological shortcomings of the three studies evaluated.

A Cochrane review [17] analysed the relationship between physical exercise and depression. An attempt was made to answer the question of whether exercise might be more effective than drugs, psychological therapy or therapeutic abstention in reducing symptoms of depression. To this end, a total of 39 clinical trials of widely differing quality were jointly analysed. The results showed that: as compared to no treatment or a control group, exercise may have a moderately beneficial effect on symptoms of depression; and as compared to pharmacological treatment or psychological therapy, no differences were in evidence (conclusions based on very few studies). In only 4 trials [18–21], which covered a total of 298 patients, was physical exercise compared to pharmacological treatment (sertraline), and no statistically significant differences were observed, though only one of these studies specifically targeted persons over the age of 65 years [21] and included only 37 of such subjects. Furthermore, in none of these studies was follow-up longer than 16 weeks. This review was an update of a previous review [22] which suggested that exercise could reduce depressive symptoms.

New research studies are needed to further detail the type of exercise that could be beneficial for older adults with depression, analyse whether such exercise could be a therapeutic alternative to antidepressants or psychological treatment, and determine the related risks and costs. Prescribing physical exercise in the consulting room, as if it was a remedy for chronic disease, calls for knowledge about which exercise is the most suitable to the task, and the duration, frequency and intensity required.

Available evidence suggests that exercise may benefit depressed patients and be comparable to antidepressant treatment [23]. It seems reasonable, therefore, for exercise to be recommended to people with depressive symptoms and those who meet diagnostic criteria for depression [24]. As yet however, the best way of implementing this recommendation in clinical practice is not known (Sonnott, 2013). It has not been possible to provide patients with accurate information about how effective exercise can be, the relative benefits of aerobic, resistance or combined exercise, whether it is better to do such exercise individually or in a group, and the optimal duration of a session. Hence, to obtain a more accurate idea of the effect of exercise on depression among older adults, there is a need for new trials based on scientifically solid methodology, an adequate number of participants, and a sufficiently long follow-up.

The aim is to ascertain the non-inferiority of supervised physical exercise to antidepressant drug treatment in terms of reducing depressive symptoms among patients presenting with clinical criteria of a depressive episode (International Classification of Diseases -10th revision/ICD-10) diagnosed in primary care.

## Methods

### Study design and setting

This will take the form of a randomised clinical trial (Fig. 1) to be conducted at health centres in the Albacete Health Area (Spain).

### Characteristics of participants

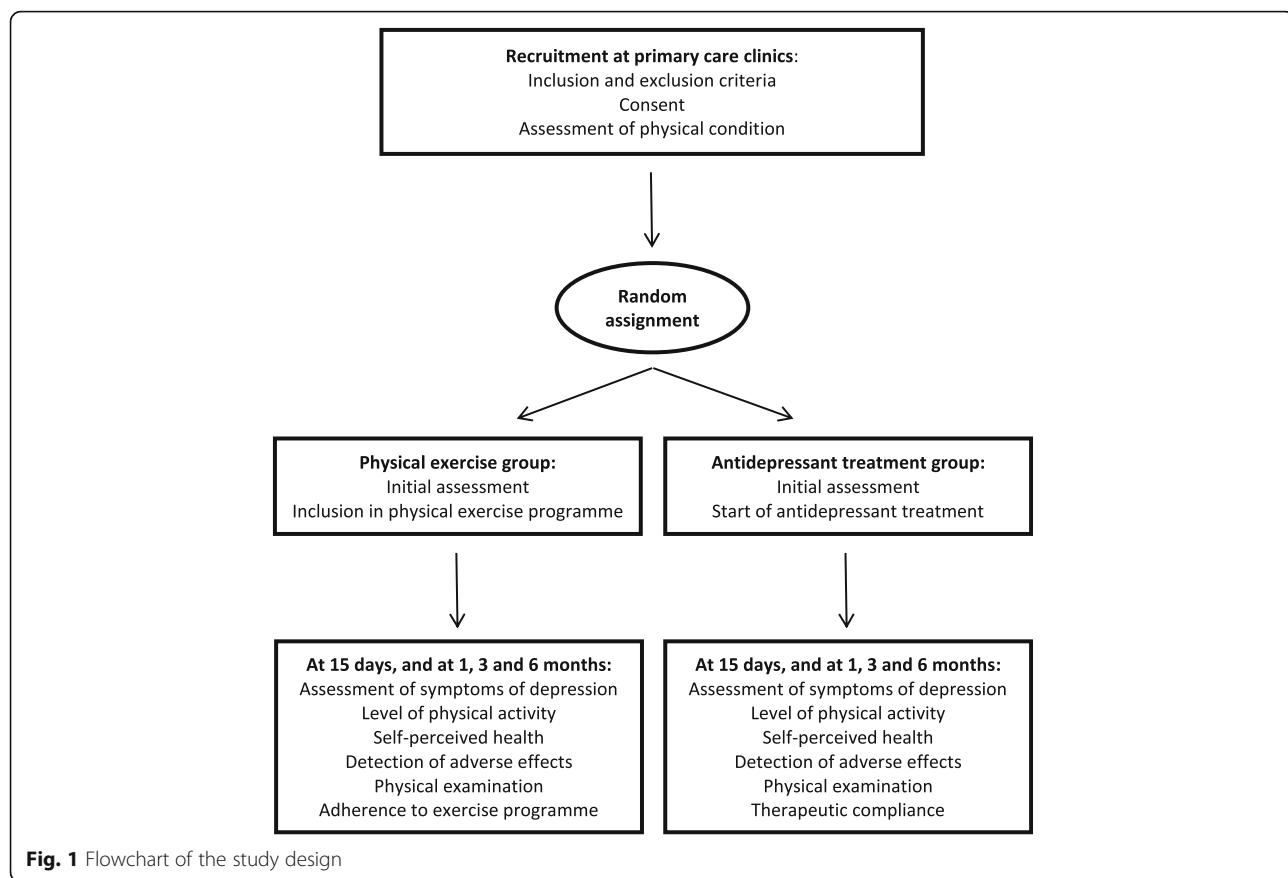
The target population will be subjects aged over 65 years with clinical criteria of a “clinically significant” depressive episode. We intend to use the ICD-10 criteria, which require a minimum of 4 out of 10 symptoms, including at least 2 of the following 3, namely, depressed mood, anhedonia and loss of energy. The 10 symptoms include: depressed mood; loss of interest or pleasure; loss of or increase in weight; insomnia or hypersomnia; agitation or slowing of movements; fatigue or loss of energy; feelings of inadequacy or guilt; poor concentration; poor self-esteem; and recurrent thoughts of death. The duration of the episode must be a minimum of two weeks.

The inclusion criteria will be the following: subjects with the above criteria of mild or moderate depressive episode belonging to the participating health centres. The exclusion criteria will be: physical or mental limitations that bar participation in the study; contraindications for doing physical training (unstable angina, arterial hypertension with systolic blood pressure > 200 or diastolic blood pressure > 110 mmHg, orthostatic hypotension > 20 mmHg accompanied by symptoms, left ventricular outflow tract due to severe/moderate aortic stenosis or obstructive hypertrophic myocardopathy, supraventricular or ventricular arrhythmias with haemodynamic deterioration not controlled with treatment, decompensated heart failure, third-degree atrioventricular block without pacemaker implantation, and important orthopaedic problems); patients with severe depressive disorder (important interference in social or occupational functioning, psychotic symptoms, active suicidal ideation or situations of personal abandonment); depressive disorders due to a medical or substance-induced disease, depressive disorders in partial or total remission and unspecified depressive disorders; subjects with evidence of a high level of physical activity according to the International Physical Activity Questionnaire (IPAQ); and patients taking antidepressant drugs.

In all participants, initial physical condition will be measured by determining their resting heart rate with a heart-rate monitor and their submaximal heart rate, calculated from the maximum heart rate (220 - age) on an exercise bicycle (70–85% of maximum heart rate at a constant workload and speed for 6 min), electrocardiogram, and flexibility (using the sit and reach test).

### Sample size

Based on an estimated positive response in 75% of participants (a reduction of at least 50% in pre-treatment



scores on the Montgomery-Asberg Depression Rating Scale/MADRS) in both the intervention (supervised physical exercise) and control groups (antidepressant therapy), an alpha risk of 0.025, a beta risk of 0.20, a non-inferiority margin of 15% (maximum difference of response for it to be deemed not inferior to the experimental treatment) and a percentage loss of 20%, a total of 156 patients will be required in each group ( $n = 312$ ).

Participants will be consecutively selected at 20 family medicine clinics belonging to 3 health centres.

### Interventions

All participants will be observed over a period of 6 months, with assessments being made at baseline and then again at 15 days and 1, 3 and 6 months. In any case where symptoms worsen, with the patient's clinical profile progressing from mild or moderate to severe depression, the patient will be referred to a mental health department, which will then decide on the course of treatment to be followed. The trial will be deemed to have ended in the following circumstances: completion of the observation period; patient withdrawal; or withdrawal of informed consent.

Patients will be included in the intervention group (physical exercise) or the control group (antidepressant therapy) by simple randomisation generated by a computer software programme. The randomisation sequence will be concealed throughout the recruitment period.

With respect to antidepressant drug therapy, the NICE guideline holds to the general view that there is little difference among the various antidepressants in terms of efficacy. As a result, patients' physicians will decide on the most suitable drug in every case.

It will be suggested to subjects assigned to the intervention group that they participate in a physical exercise programme consisting of two 1-h sessions per week for a period of 6 months (a total of 48 sessions in groups of 10–12 persons), to be given by sports coaches and held at sports facilities.

The educational content of physical activity, based on the recommendations of the American College of Sports Medicine, will include the following: how to increase physical effort in activities of daily living; how to perform regular exercise adapted to one's age and individual condition, to help maintain ideal body weight; how to do exercise or aerobic sport; how to warm up; how to perform stretching exercises (musculotendinous stretching);

how to conduct a period of cooling-down exercises and relaxation; and how to approach muscle-strengthening and flexibility training.

Participants will be shown how to increase their levels of physical activity in daily life, with the idea that at least 30 min of average to moderately intense activity should be performed throughout the entire follow-up period on an almost daily basis. The physical exercise programme will include: aerobic exercises (goal: a minimum of 30 min of aerobic activity of moderate intensity five days per week); muscle-strengthening exercises (goal: a minimum of two non-consecutive days per week, with 10–15 repetitions of each exercise at a moderate-to-high level of intensity); flexibility exercises (goal: at least twice per week for at least 10 min); and balance-strengthening exercises (goal: at least three times per week).

The educational intervention will be conducted from a behavioural standpoint, aimed at achieving patients' understanding and acceptance, and bringing about a shift towards improvement in their habits. The following will be required: a baseline for adopting and maintaining lifestyle changes; patients' commitment to and an active role in the process; and a linear design, with consecutive phases of learning adapted to needs.

### **Study variable**

The principal outcome variable will be a reduction in depressive symptoms: a fall in the pre-treatment 10-item Montgomery-Asberg Depression Rating Scale (MADRS) and 15-item Geriatric Depression Scale (GDS) scores, with these scales being administered at baseline and subsequently at 15 days and 1, 3 and 6 months.

At baseline, the following variables will be assessed in all participants: health problems (as classified by the International Classification of Primary Care/ICPC-2); drug use (Anatomical Therapeutic Classification); toxic habits (consumption of tobacco, grams of alcohol/week and other substances); history of depressive disorders and use of antidepressant drugs; and socio-demographic characteristics (gender, age, educational level, social class based on occupation, and marital status).

At baseline and again after 15 days, 1, 3 and 6 months, the following variables will be assessed in all participants: level of physical activity (with the patient being classified as inactive, active or partially active, using the IPAQ); self-perceived health status, using the EQ-5D questionnaire (evaluating the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, as well as a visual analogue scale of self-reported health, scored from 0 to 100); anthropometric measurements (weight, height, body mass index and waist circumference); blood pressure using an

automatic digital blood pressure arm monitor; and presence of adverse events.

The following variables will be obtained in the intervention group: participants' attendance at physical-exercise programme sessions and possible reasons for withdrawal; degree of satisfaction and acceptance of the educational programme (scale of 1 to 5 points, ranging from "very dissatisfied" to "very satisfied"); and compliance with exercise recommendations using a simple tool based on self-recording of daily physical activity (this record will be used to assess the frequency, intensity, duration and type of exercise performed).

In patients who receive treatment with antidepressant drugs, the following will be assessed: type of antidepressant (N06A Group Anatomical Therapeutic Classification); changes in treatment across the follow-up period; adherence (Morisky-Green questionnaire); and treatment satisfaction (Satisfaction with Antidepressant Treatment Questionnaire - *Cuestionario de Evaluación de la Satisfacción con el Antidepressant treatment/ESTA*).

The cost-effectiveness analysis will take into account the direct costs of both the exercise and antidepressant-treatment programmes, including staff expenses, medication, follow-up visits and monitoring.

### **Statistical analysis**

All statistical analyses will be performed on a blinded basis so as to ensure that the respective subjects' group affiliations remain unknown to the assessor. After the preliminary stages of debugging, exploratory analysis, and variable categorisation or transformation have been completed, variables of interest, stratification of variables and potential confounding at baseline in the two groups will be compared, and the homogeneity of the study variables' baseline values will be checked. An intention-to-treat analysis will be used to calculate the following parameters with their corresponding confidence intervals: absolute increase in benefit; relative increase in benefit; and number needed to treat.

The trend in the parameters of interest in the two groups will be described and compared (comparison of proportions and means in independent groups). An analysis by subgroup will be performed according to different variables, including sex, intensity of physical activity, adherence to recommendations, etc.

Finally, the effect of the intervention in terms of reducing depressive symptoms will be estimated using a logistic regression model, with statistical adjustment between possible confounding and interaction terms. The model will be interpreted on the basis of the statistical significance of the coefficients and the value of the odds ratios of the explanatory variables.

## Discussion

The results could be useful when it comes to finding a better and more effective approach to a health problem that is prevalent among older adults, and reducing the related disease burden on society as a whole. In terms of the number of patients and duration of follow-up, the proposed clinical trial is a project which easily surpasses the few studies on this subject that have been previously conducted on the elderly. Its aim is to provide scientific evidence on a therapeutic resource -physical exercise- which has undeniable health benefits and can be applied to certain health problems, such as depressive disorders, which are of great magnitude and considerable socio-economic relevance, and have a significant impact on the quality of life of older adults.

The project will make it possible to establish the type of specific physical exercise recommendations that are capable of reducing depressive symptoms among older people who meet clinical criteria for depressive disorders. Furthermore, the duration, frequency and intensity needed to ensure an efficacy similar to that of available drug treatments will be determined, thereby remedying some of the shortcomings present in the studies undertaken to date.

Should the hypothesis prove to be true, engaging in physical exercise could be regarded as a novel therapeutic resource in primary care for treating depression in older adults, and be incorporated into clinical practice guidelines along with the currently recommended pharmacological or psychotherapeutic treatments. This new therapeutic resource could have a favourable impact on the health and wellbeing of older adults, and serve to reduce health-care costs.

Among the obstacles to achieving the designated goals, mention should be made of the difficulty of conducting a trial with a high number of patients of advanced age, the need for adequate co-ordination among the different professionals, and the necessary adherence to the physical exercise programmes by the participants in order to obtain the expected benefits. The estimated sample size has been increased by 20% to offset the foreseeable loss of subjects across follow-up. Furthermore this is an open trial, seeing as what is being tested here is not a pharmacological intervention but a six-month-long physical activity programme, something that renders the use of masking techniques inviable. Even so, it is envisaged that all statistical analyses will be performed on a blinded basis, to ensure that the respective subjects' group affiliations remain unknown to the assessor and thereby reduce any likelihood of the assessment of the effects of the intervention being biased.

In sum, it will enable the approach taken to depressive disorders in clinical practice to be changed, by offering a therapeutic alternative to existing

treatments, unencumbered by the numerous adverse effects of antidepressant therapy and capable of reducing the frequent polypharmacotherapy of older adults. In addition, the benefits of exercise can be extended to the cardiovascular area and musculoskeletal disorders, thus contributing decisively to more active ageing and a better overall level of health.

## Abbreviations

EQ-5D: EuroQol 5 Dimensions; ESTA: Questionnaire for the Evaluation of Antidepressant Treatment Satisfaction; GDS: Geriatric Depression Scale; HR: Heart rate; ICD: International Classification of Diseases; ICPC: International Classification of Primary Care; IPAQ: International Physical Activity Questionnaire; MADRS: Montgomery-Asberg Depression Rating Scale

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## Availability of data and materials

Not applicable because this is a study protocol.

## Authors' contributions

JLTH, FER, JMTL, MJML, KNR, CBG, JFM, VFL and MALC are the investigators responsible for project design and protocol writing. JLTH, MALV and JRS have participated in sample size calculation and statistical analysis planning. JLTH, JaTTL, JeTTL, LAS, MCR, JFM, ALY, JMN, CSC, IRG, CBG, JLEB, CEV and ALG have contributed to study background, general design and study

variable definition. All authors have contributed to the preparation of the project and have read and approved the final manuscript.

#### Ethics approval and consent to participate

This project was approved by the Research Ethics Committee of the University Hospital of Albacete on 26 June 2014. The subjects selected will be provided with oral and written information of the study objectives and will be asked to sign the consent form before participating.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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(number of cohorts born before and after the reform) and focus on respondents born 48 months before or after the cut-off for eligibility to the reform (n=18 928).

To document the impact of the reform on school leaving age we use the French Labor Force Survey (LFS), a household survey representative of the French population living in private households. We use data on the age at which respondents left full-time education measured in the 2012 wave. We include respondents born within 48 months of the reform, which includes 72 133 individuals.

## Outcomes

In Constances, mental health was measured using the 20-item version of the Centre for Epidemiologic Studies Depression scale (CES-D),<sup>24</sup> a validated depressive symptoms scale. Higher scores indicate higher levels of depressive symptoms and a cut-off of 16 for men and 20 for women was used to define elevated levels of depressive symptoms.<sup>25</sup>

Cognitive function was assessed by trained neuropsychologists using five tests.<sup>26</sup> The Mini-Mental State Examination (MMSE) is a general test of cognitive function consisting of 30 questions assessing five areas of cognition: orientation, registration, attention and calculation, recall and language. The Digit-Symbol Substitution Task of the Wechsler adult intelligence scale IV assesses psychomotor speed. The respondents were presented with nine digit-symbol pairs, followed by a list of numerical digits. They were asked to write the corresponding symbol under each digit as fast as possible. We retain the number of symbols correctly associated in 90 s.<sup>27</sup> The Free and Cued Selective Reminding Test (FCSRT) measures verbal episodic memory. Respondents were first asked to read and memorise 16 words, then asked to recall as many words as possible in 2 min. The neuropsychologist provided a cue for each word that has not been retrieved. For this study, we include the FCSRT free immediate recall score. Finally, two verbal fluency tasks were included to assess language abilities: number of words related to the ‘animals’ category named in 1 min for the semantic fluency task and number of words starting with the letter ‘R’ named in 1 min for the phonemic fluency task. As the scale of each individual cognitive test differs, each score is converted to a z-score by subtracting the mean and dividing by the SD. A global cognitive score is obtained by summing the standardised tests. High cognitive performance is defined as the top quartile of the global score’s distribution.

Physical functioning is assessed based on three objective health measures. Hand grip strength was assessed using a handheld dynamometer. Participants were asked to sit and squeeze the dynamometer for a few seconds with their dominant hand. The exercise was repeated three times and grip strength was determined as the average of the three results. Finger tapping, a measure of motor performance, was assessed by the number of taps respondents could do with the index finger of their dominant hand for 15 s. Walking speed was measured as the time taken by respondents to walk 3 m at a rapid pace. For each physical health outcome, high levels of physical functioning are defined based on the top quartile of the distribution.

## Years of schooling and completed education

Schooling is measured as the age at which respondents left full-time schooling (in the French LFS) and the highest level of education completed (in the Constances data). Educational attainment in Constances is reclassified into four categories: primary education or less, lower secondary education, upper secondary education and tertiary education.

## Parental socioeconomic position

Parental SEP during the respondent’s adolescence is based on the French classification of professions and socioprofessional categories. It is recategorised into high (managerial, professional occupations), intermediate (trade and services related occupations) and low parental SEP (manual occupations).

## Analysis design

We implement a Regression Discontinuity Design (RDD), a quasi-experimental approach used to isolate the causal effect of an exposure using observational data.<sup>28</sup> It aims to address unmeasured confounding and reverse causality by exploiting the discontinuity in schooling duration generated by the reform across otherwise similar cohorts. The reform raised the minimum school leaving age for all children born after 1 January 1953 from 14 to 16 years. Our approach classifies respondents born after this cut-off date as the eligible group, while respondents born prior to the cut-off were classified as the ineligible comparison group. RDD compares outcomes between these groups, appropriately accounting for secular trends using local linear regression.

Because some respondents would have stayed at school beyond the age of 14 in the absence of the reform, we implement a fuzzy RDD and estimate an intent-to-treat effect. Our estimates do not capture the impact of additional schooling per se, but the impact of eligibility to a policy that requires students to stay until age 16 at school. Our main model specification is as follows:

$$Health_{ict} = \gamma_0 + \gamma_1 D_{ic} + f(R_{ic}) + \gamma_2 X_{ict} + u_{ict} \quad (1)$$

where  $Health_{ict}$  is a health outcome measure for individual  $i$  from birth cohort  $c$  at time  $t$ ;  $D_{ic}$  is a binary variable taking the value of 1 if an individual was born after the cut-off date, and of 0 if the individual was born prior to this date;  $R_{ic}$  is an individual’s birth cohort relative to 1 January 1953 measured in months, which aims to capture secular trends and  $X_{ict}$  is a vector of individual characteristics: age, age squared, gender and month of birth. The coefficient  $\gamma_1$  denotes the health effect of being eligible to the reform. Using local linear regression we model birth cohort effects as a piecewise linear function, with different slopes on each side of the cut-off date.

We explore heterogeneous effects by first stratifying our models by gender and parental SEP and then interacting the reform dummy with these variables. Ordinary least squares regressions are used to obtain coefficients and 95% CIs for continuous scores and logistic regressions for OR and 95% CIs for dichotomous outcomes. SEs are clustered at the month of birth level, as recommended when the variable which determines eligibility is discrete.<sup>29</sup> To ensure that the functional form is correctly specified, we also estimate models with a cubic term for age. Additional models using triangular kernel weights are estimated to test whether our findings are robust to giving more weights to observations which are closer to the cut-off for eligibility. All analyses were carried out using Stata V.14.

## RESULTS

**Table 1** presents basic characteristics for respondents in our analytical sample (n=18 929). 9635 respondents (mean age=63.68 years) were born up to 48 months before the policy and constitute our ineligible group, while 9293 respondents (mean age=59.72 years) were born up to 48 months after the policy and compose our eligible group. Pre-reform characteristics are similar across the two groups. Additional descriptive statistics are provided in online supplementary appendix table 1.

**Table 1** Sample characteristics by eligibility status in the 2012 Constances study (n=18 929)

	Percentage*		
	Ineligible (born before the 1 January 1953) (n=9635)	Eligible (born after the 1 January 1953) (n=9293)	Difference (p value)
Mean age (SD)	63.68 (1.65)	59.72 (1.65)	<0.001
Gender			0.10
Male	48.75	48.01	
Female	51.25	51.99	
Father's SEP during adolescence			0.19
High SEP	14.86	15.47	
Intermediate SEP	38.99	38.77	
Low SEP	46.14	45.75	
Father's region of origin			0.09
France (mainland and overseas territories and departments)	84.65	84.70	
Europe	8.40	7.94	
Northern Africa	3.87	4.50	
Other	3.08	2.86	
Educational attainment			0.17
Primary	3.35	3.24	
Secondary	53.96	53.99	
Tertiary	42.70	42.77	
Respondent's SEP			0.12
High SEP	31.82	28.35	
Intermediate SEP	57.82	60.39	
Low SEP	10.36	11.26	

\*Percentages unless otherwise indicated. Only respondents born within 48 months of the cut-off are included in our sample.

SEP, socioeconomic position.

Online supplementary appendix figure 1 shows a strong educational gradient in mental and cognitive health in our sample, with higher educated respondents enjoying higher cognition and lower levels of depressive symptoms. A less pronounced association was found for finger tapping. There is no apparent relationship between educational attainment and grip strength or gait speed in our sample.

Figure 1 displays the effect of eligibility to the reform on the proportion of respondents who left school after the age of 16 by gender and birth cohort in the French LFS. There is a clear discontinuity—an increase larger than expected based on the modelled trend—at the time of the reform. Table 2 indicates that the reform increased the time spent at school by 2.76 months for men (95% CI 1.45 to 4.29) and by 2.88 months for women (95% CI 1.40 to 4.36). It was also associated with higher odds of leaving school after the age of 16 for both men and women. Supplementary analyses (online supplementary appendix table 2) show that the effect is concentrated among participants from disadvantaged backgrounds (p value for interaction term <0.001).

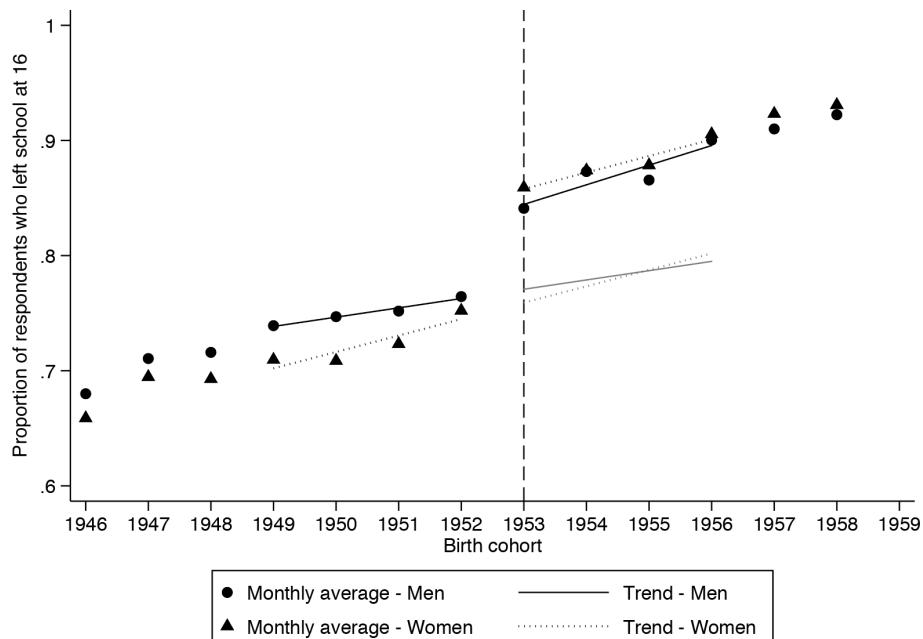
Figure 2 presents the effect of eligibility to the reform on each health outcome by gender and birth cohort. There is an apparent discontinuity in cognitive scores for men and depressive symptoms for women for the 1953 cohort, suggesting that the reform may have increased cognition in men but also depressive symptoms scores among women. Table 3 presents local regression estimates of the effect of the reform on health. Males required to stay at school longer had higher cognitive scores ( $\beta=0.15$ , 95% CI 0.06 to 0.24) and higher odds of being in the top quartile of cognitive performance (OR=1.81, 95% CI 1.26 to 2.66) compared with those who were permitted to leave school at age

14. Results by individual cognitive score (online supplementary appendix table 3) show that this effect was driven by higher scores on the MMSE and memory test. Eligibility to the reform had no effect on depressive scores or physical functioning among men.

Among women, there are no significant effects of eligibility on cognition overall or on specific cognitive tests (online supplementary appendix table 3). The p value for the interaction term between eligibility to the policy and gender is significant ( $p=0.03$ , online supplementary appendix table 4). However, women eligible to the reform scored 1.52 points (95% CI 0.33 to 2.71) higher on the CES-D depression scale and had higher odds of elevated depressive symptoms (OR=1.27, 95% CI 1.05 to 1.54). We find no effect of the reform on women's physical functioning.

Supplementary analyses stratified by parental SEP (online supplementary appendix table 5) indicate that these effects are concentrated among respondents from disadvantaged families although the interaction term between eligibility to the reform and low parental SEP is not significant either for cognition ( $p=0.12$ ) or depressive symptoms ( $p=0.18$ , online supplementary appendix table 4). Additional analyses on intermediate socioeconomic outcomes indicate that the reform did not translate into higher qualifications or wages for either gender but was associated with higher odds of being in employment in 2012 among men (online supplementary appendix table 6). The reform was also not associated among women with marital status or number of children (online supplementary appendix table 7).

We conducted several sensitivity analyses to check the robustness of our findings.<sup>30</sup> First, our results on cognition and depressive symptoms are robust to the inclusion of a cubic term for age



**Figure 1** Effect of eligibility to the 1959 Berthoin reform on the proportion of respondents who left school after 16 by gender in the 2012 French Labor Force Survey (n=72 133), Birth cohorts 1946–1959. The dots and triangles show the average school leaving age, respectively, for men and women and for each birth cohort. The dashed line represents the cut-off for eligibility to the reform (1 January 1953). The fitted lines represent the linear trends for our analytical sample: respondents born up to 48 months before or after the reform, separately for men (black lines) and women (dotted lines). The grey fitted lines show the predicted school leaving age in the absence of the reform.

(online supplementary appendix table 8) and to an alternative estimation with triangular kernel weights (online supplementary appendix table 9). Second, to confirm that our estimates are driven by the reform and not by secular trends, we estimate the effect of ‘placebo reforms’ for years in which the reform did not take place (online supplementary appendix figure 2). Analyses revealed no evidence of other discontinuities for cognition among men and for depressive symptoms among women. Third, we experiment with different bandwidths, ranging from 12 to 72 months. Results presented in online supplementary appendix figure 3 indicate that our estimates are also robust to different bandwidth sizes.

## DISCUSSION

We leverage the discontinuity in schooling duration induced by a major French reform to estimate the long-term effects of schooling on adult health. Our results offer a complex picture: while men who stayed longer in school as a result of the reform had better cognitive function in older age, women eligible to

reform did not show gains in cognitive function and instead displayed higher levels of depressive symptoms in midlife.

### Effects on cognition

Our findings are consistent with previous evidence of long-term positive effects of schooling reforms on memory scores,<sup>3,4</sup> in particular among men.<sup>31</sup> These findings suggest that increased schooling may increase cognitive reserve and thus postpone the manifestation of cognitive decline in later life.<sup>32</sup> These effects were confined to men, which might be in part due to the relatively young age of respondents in our sample: women have lower incidence of dementia before 75 and are less affected in early old age by vascular midlife risk factors than men.<sup>33</sup>

### Effects on mental health

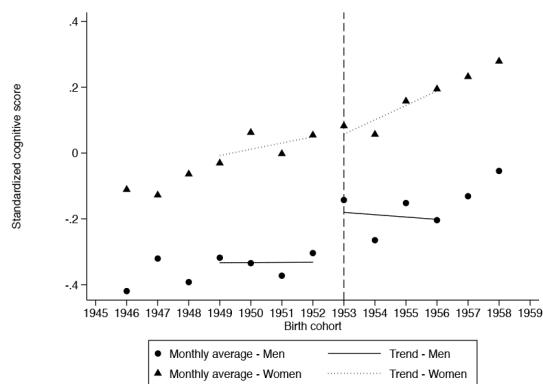
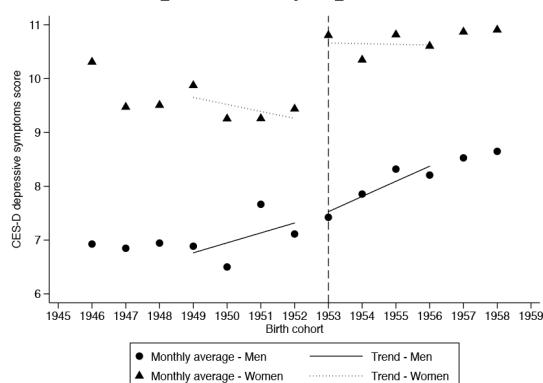
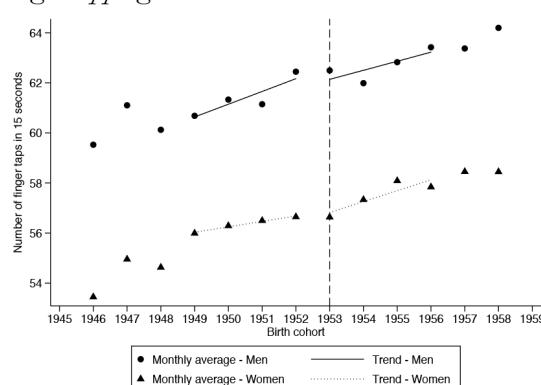
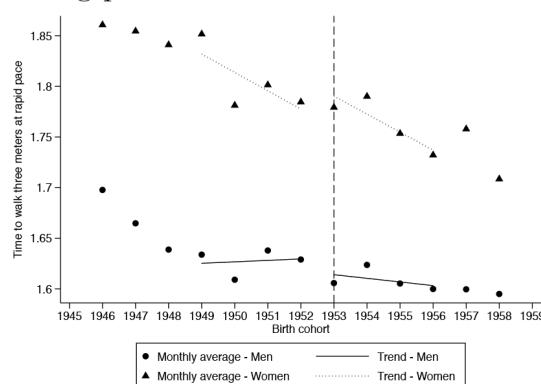
Eligibility to the reform was associated with higher levels of depressive symptoms among women. We found a clear association between educational attainment and depressive symptoms

**Table 2** Effect of eligibility to the 1959 Berthoin reform on average school leaving age and odds of leaving school after the age of 16, by gender and parental SEP during adolescence in the 2012 French Labor Force Survey (n=72 133)

	Men				Women			
	$\beta$	95% CI	OR	95% CI	$\beta$	95% CI	OR	95% CI
All respondents	0.24	0.12 to 0.36	1.49	1.30 to 1.70	0.24	0.12 to 0.36	1.93	1.69 to 2.21
High parental SEP	-0.03	-0.52 to 0.46	0.84	0.27 to 2.62	-0.222	-0.63 to 0.18	1.012	0.33 to 3.11
Intermediate parental SEP	0.03	-0.23 to 0.29	1.06	0.80 to 1.39	0.098	-0.07 to 0.27	1.58	1.25 to 1.99
Low parental SEP	0.33	0.19 to 0.47	1.69	1.47 to 1.96	0.353	0.19 to 0.52	2.05	1.76 to 2.39

The ordinary least square estimates measure the effect of the reform on average school leaving age while ORs measure the effect of the reform on the odds of leaving school after the age of 16. All models control for age, age squared, month of birth, birth cohort relative to the cut-off point, interacted with the treatment. SEs are clustered at the month of birth level. The bandwidth is fixed at 48 months.

SEP, socioeconomic position.

**A Standardized cognitive score****C Physical functioning measures***Hand grip strength***B CES-D depressive symptoms score***Finger tapping**Walking speed*

**Figure 2** Effect of eligibility to the 1959 Berthoin reform on health outcomes by gender in the 2012 Constances Study ( $n=33\ 762$ ), Birth Cohorts 1946–1959. The dots and triangles show the average school leaving age, respectively, for men and women and for each birth cohort. The dashed line represents the cut-off for eligibility to the reform (1 January 1953). The fitted lines represent the linear trends for our analytical sample: respondents born up to 48 months before or after the reform, separately for men (black lines) and women (dotted lines). CES-D, Center for Epidemiologic Studies Depressive Symptoms Scale.

in our sample for both genders.<sup>34</sup> However, the sign reversed for women once we implemented an RD design exploiting the change in schooling duration. This result echoes findings from recent quasi-experimental studies in Sweden, Great Britain and Turkey<sup>15 16 35</sup> reporting negative effects of schooling on mental health and emotional well-being. A recent review concluded that evidence of a positive effect of schooling on women's health is overall weaker than for men.<sup>22</sup>

There are several possible explanations for these results. Education is hypothesised to influence health partly by enhancing access to health-promoting resources such as health literacy, self-efficacy, social networks and better jobs and earnings.<sup>1</sup> Available evidence suggests that the French reform—contrary to other schooling laws in the USA and Western Europe—did not lead to substantive improvements in qualifications or earnings.<sup>36</sup> Our analyses partly confirm this pattern: longer schooling

**Table 3** Effect of eligibility to the 1959 Berthoin reform on health outcomes by gender in the 2012 Constances study (n=18929)

	Men				Women			
	$\beta$	95% CI	OR	95% CI	$\beta$	95% CI	OR	95% CI
Cognitive score	0.15	0.06 to 0.24	1.81	1.26 to 2.66	-0.01	-0.13 to 0.12	0.84	0.60 to 1.13
CES-D score	0.22	-0.73 to 1.17	1.05	0.83 to 1.32	1.52	0.33 to 2.71	1.27	1.05 to 1.54
Hand grip strength	0.07	-0.88 to 1.02	1.02	0.82 to 1.27	-0.73	-1.51 to 0.05	0.07	0.01 to 1.04
Finger tapping	-0.55	-1.95 to 0.85	0.89	0.65 to 1.21	0.05	-1.37 to 1.47	1.30	0.86 to 1.99
Walking speed	-0.01	-0.05 to 0.02	0.74	0.53 to 1.02	0.02	-0.02 to 0.06	1.04	0.76 to 1.43

ORs measure the odds of being in the top quartile of cognitive and physical functioning and of reporting elevated depressive symptoms based on the CES-D recommended cut-off. All models control for age, age squared, month of birth, birth cohort relative to the cut-off point, interacted with the treatment. Standard errors are clustered at the month of birth level. The bandwidth is fixed at 48 months.

CES-D, Centre for Epidemiologic Studies Depression score.

did not translate into higher qualifications or wages for either gender but was associated with higher odds of being in employment in 2012 among men. For women, the additional years of schooling were not associated with an upgrading of their position in the labour market, potentially creating a job-education mismatch detrimental for mental health.<sup>37</sup> The discrepancy between the expectations created by the reform and the actual long-term benefits might have been particularly harmful for women's mental health as research suggests that women have smaller economic returns on education.<sup>38</sup> A second hypothesis is that the health effects of education for women operated partly through the marriage market and not exclusively through employment and wages.<sup>22 39</sup> However, the reform did not exert any effects through this pathway as eligibility was not associated with women's marital status or number of children.

### Effects on physical functioning

Consistent with our findings for physical functioning, previous studies have reported weak or inconsistent effects of schooling laws on physical health.<sup>40</sup> There are three possible interpretations. First, we may not have enough power to detect the effect of the reform on physical health: the CIs for these estimates are wide and include substantial benefits as well as harms as plausible effects. Second, our sample was relatively young and these measures may not discriminate subtle differences in physical functioning in younger age. A third possible interpretation is that the commonly observed association between education and functioning may be partly driven by selection. A potential implication would be that increasing compulsory schooling may not be an effective policy to improve physical health. A recent theoretical framework linking human capital, schooling and health identified skills formation as a critical pathway.<sup>22</sup> Our results indicate that degree attainment and skill formation—which were not impacted by the Berthoin reform—might be more important for health than the amount of time spent in school.

### Strengths and limitations

Major strengths of our study include the use of a quasi-experimental design in a large population-based cohort, as well as an extensive battery of objective health measures. RDD is a powerful tool to estimate causal effects of policies for which eligibility is based on a clearly defined threshold or time point.<sup>28</sup> A limitation is that our data are cross-sectional, so we were unable to examine longitudinal trajectories. Reverse causality, however, is not a concern in our study because the reform affected cohorts decades before health measures were taken. In addition, if exposure to the policy is 'as good as' random, using cross-sectional data should not compromise estimates of the impact of the policy on health outcomes in later life.

Taken together, our findings provide a mixed picture of the long-term health effects of a policy that increased compulsory schooling. Decades after implementation, the Berthoin reform led to better cognitive outcomes among men, but also to increased rates of depressive symptoms among women. The reform had no measurable impact on physical functioning. Our results do not suggest that education is not beneficial for health but indicate that policies focused on increasing the quantity of schooling and not its quality, for example, might not be the best tool to improve population health.

### What is already known on this subject

- Education is a social determinant of health particularly amenable to public policy reforms.
- Observational studies have suggested that higher education is associated with better health but whether policies that increase schooling duration can also improve health is unclear.

### What this study adds

- Our findings provide new quasi-experimental evidence on the long-term effects of compulsory schooling on a range of adult clinical outcomes.
- An increase in compulsory schooling was associated with large increases in cognition among men and also with increased depressive symptoms among women.
- These results highlight the need to consider the potential trade-offs of schooling laws as tools to improve population health.

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**Data sharing statement** The Constances cohort is available for registered users and on approval of a research project by the scientific board at [http://www.constances.fr/index\\_EN.php](http://www.constances.fr/index_EN.php).

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Method
<b>Participants</b>
We used data from English Longitudinal Study of Ageing (ELSA): a large, longitudinal cohort study representative of the English population of people aged $\geq 50$ years established in 2002. <sup>23</sup> The study received ethical approval from the National Research Ethics Service and all participants gave informed consent. We specifically worked with data from wave 2 (2004/2005) across every biennial wave through to wave 7 (2014/2015); a total of six waves and a decade of data.
<b>Measures</b>
Cultural engagement
Our measurement of cultural engagement used self-reports by participants at wave 2 and consisted of three items asking about the frequency of visits to (a) the theatre, concerts or opera, (b) the cinema and (c) an art gallery, exhibition or museum. We combined responses from these three variables to create an overall frequency of receptive cultural engagement, with responses coded as never, less than once a year, once or twice a year, every few months, about once a month or twice a month or more. Because of the small sample size in the two most frequent visits categories, we collapsed these to provide an overall five-point scale.
Depression
Depression was measured in two ways. First, we used the Centre for Epidemiologic Studies Depression Scale (CES-D), a widely used self-report measure of depressive symptoms used to identify people at risk of developing depression in the general population. <sup>24</sup> We specifically used the 8-item version, which has been found to have comparable psychometric properties with the full 20-item scale. <sup>25</sup> Each item assesses negative affect symptoms or somatic complaints experienced in the past week using a binary reporting scale, with the total number of symptoms summed (0–8). Previous studies using the eight-item CES-D have used a score of three or greater to denote the presence of depression, and this cut-off has been validated against standardised psychiatric interviews with older adults. <sup>25</sup> To identify whether participants scored above the threshold for depression at any of the waves across the 10 years, we assessed their overall CES-D score at all waves and if a score was three or greater at any wave, they were classed as having experienced a depressive episode.
The second way participants were identified as having experienced depression was if they reported that a doctor had diagnosed them with depression in the 2 years between each wave. This allowed us to identify participants where CES-D scores might have been raised between waves but were recovered by the point of assessment either through intervention (such as antidepressants or counselling) or otherwise.
Covariates
We obtained information from wave 2 (baseline) on sociodemographic, health-related and social variables likely to confound associations between exposure and outcome. Sociodemographic covariates included age, gender, ethnicity (coded as White or Black and minority ethnic as ELSA is predominantly White British) and relationship status (in a couple versus without a partner). Socioeconomic position was assessed with net non-pension wealth quintiles, highest educational attainment (no qualifications; educational qualifications at age 16; educational qualifications at age 18; further educational qualifications) and employment status (full time; part time; not in employment).
In relation to participants' health and health behaviours, we assessed whether participants had a chronic/long-standing illness (including cancer, chronic obstructive pulmonary disease, diabetes, angina or a previous stroke), whether they had self-reported problems with eyesight or hearing likely to hinder their participation in cultural activities, and whether they had moderate or severe pain. We also measured self-reported alcohol intake (every couple of months or less; once or twice a month; 1–4 days per week; $\geq 5$ days per week). In addition, we excluded participants registered as blind ( $n = 3$ ) or reporting major difficulties with mobility (unable to walk 91.4 m (100 yards) or sit for 2 h, $n = 460$ ).
For social variables, we measured social engagement using a composite score of how often participants had contact (whether face to face, over the phone or over email) with friends, children or wider relatives. We assessed whether participants were engaged in any civic activities (including being a member of a political party or environmental group, a tenants or neighbourhood watch group, a church or religious association, a charitable association, an education, arts or music class, a social club, a sports, gym or exercise class or any other society). We also recorded whether participants reported having a hobby or pastime, or reading a daily newspaper.
<b>Statistical analysis</b>
Incidence rates of depression over the 10 years were computed by frequency of cultural attendance per 100 person-years, calculating the time to onset of depression measured biennially. We then used logistic regression analyses to calculate the odds ratio (OR) and 95% confidence intervals that over the 10 years of follow-up participants experienced a depressive episode. Model 1 adjusted for baseline subclinical CES-D score and demographic covariates: age, gender, marital status, ethnicity, educational attainment, employment status and wealth. Model 2 additionally adjusted for health and health behaviour covariates: eyesight, hearing, chronic health conditions, pain and alcohol consumption. Model 3 additionally adjusted for social covariates: social networks, civic engagement, having a hobby or pastime or reading a daily newspaper. To test for trend, we also modelled cultural engagement as a five-point continuous score, where the odds ratios represent a one-unit change in frequency of engagement.
For all analyses, because of the possibility of left-censoring, whereby participants could enter the study having had depression for many years and have different profiles of cultural engagement, we excluded all participants who had above-threshold depressive symptoms at baseline, who reported visiting a doctor about depression in the 2 years prior to our baseline, who had taken antidepressants or had counselling for depression in the 2 years prior to baseline, or who had an ongoing or recent (past 2 years) diagnosis of any other psychiatric condition ( $n = 335$ ).
We ran a number of sensitivity analyses to test the assumptions of our analyses. We first weighted all data using baseline cross-sectional weights derived from ELSA to ensure the sample was representative of the English population and to account for differential non-response across the following 10 years based on demographic predictors.
The second set of sensitivity analyses explored whether analyses were affected by subclinical symptoms of depression at baseline that might have affected their patterns of cultural engagement or predisposed them to developing depression over the follow-up period by (a) excluding all participants who reported feeling depressed for much of the time over the past week at baseline (even if they had not reported a depression diagnosis or an above-threshold CES-D

score); and (b) excluding participants who had a CES-D score of two at baseline indicating possible subclinical symptoms.

The third sensitivity analysis explored the possibility of reverse causality (whereby precursors to the development of depressive symptoms may alter/reduce participation in cultural activities), by conducting a subgroup analysis excluding participants who developed depressive symptoms in the first wave following baseline.

The fourth sensitivity analysis tested whether excluding those with depression at baseline led to a biased sample, so we re-ran analyses including the 335 participants who already had depressive symptoms or a diagnosis of depression at baseline, which allowed us to assess whether cultural participation was associated with the development or continuation of depressive symptoms.

The fifth sensitivity analysis tested the assumption of a threshold of  $\geq 3$  on the CES-D scale: as another study has suggested a threshold of  $\geq 4$  for identifying people with elevated depression<sup>26</sup> we re-ran our analyses using this threshold.

Finally, in order to ascertain whether cultural engagement was merely a proxy for having a more open personality type, which itself might have been protective against developing depression, we also controlled for personality using the Midlife Development Inventory personality scale.<sup>27</sup> Sensitivity analyses are shown in supplementary Tables 1–6 available at <https://doi.org/10.1192/bj.2018.267>. All analyses were carried out using Stata SE Version 14.1.

## Results

### Description of the participants

Our sample included a total of 2148 participants. The frequency distribution for the demographic characteristics of the participants is presented in Table 1, along with descriptive data of frequency of cultural engagement. Participants had a mean age of 62.9 years (range 52–89). In total, 74.8% participants reported going to a gallery or museum at least once a year.

### Rate of depression by cultural attendance

At baseline, all participants were below the threshold for depression on CES-D, but over the next 10 years, 616 participants (28.7%) recorded a CES-D score above the threshold for depression or reported having been diagnosed since the last wave on at least one occasion. The overall incidence rate was 3.31 (95% CI 3.06–3.58) per 100 person-years. There was an above-average incidence rate for those who never engaged with culture or engaged only infrequently (up to once or twice a year) (Table 2). However, more frequent attendance (every few months or more) was associated with a below-average incidence rate.

### Logistic regression analysis

Engaging with culture every few months or more was associated with a reduced risk of developing depression across the 10 years, independent of demographic factors (model 1), additional health-related factors and behaviours (model 2), and additional social and civic engagement (model 3). There was evidence of a dose-response relationship with more frequent attendance associated with a lower risk. For fully adjusted models, this equated to a 32% lower risk of developing depression for people who attended every few months ( $OR = 0.68$ , 95% CI 0.47–0.99,  $P = 0.046$ ) and a 48% lower risk for people who attended once a month or more ( $OR = 0.52$ , 95% CI 0.34–0.80,  $P = 0.003$ ) (Table 3).

Tests for trend were significant ( $OR = 0.87$ , 95% CI 0.79–0.95,  $P = 0.002$ ). Less frequent attendance (just once or twice a year) appeared to be associated with a reduced risk of depression when

**Table 1** Participant demographics

Covariates all measured at wave 2 ( <i>n</i> = 2148)	Values
Gender: women, <i>n</i> (%)	1108 (51.6)
Age, years: mean (s.d.)	62.9 (7.5)
Ethnicity, Black and minority ethnic: <i>n</i> (%)	19 (0.9)
Relationship status, in relationship: <i>n</i> (%)	1669 (77.7)
Education, <i>n</i> (%)	
NVQ1/CSE or no qualification	547 (25.5)
NVQ2/GCE O level	470 (21.9)
NVQ3 A level/higher education	710 (33.1)
Degree	421 (19.6)
Employment status, <i>n</i> (%)	
Not working/retired	1119 (52.1)
Part time	428 (19.9)
Full time $\geq 35$ h/week	601 (28.0)
Health-related issues	
Eyesight problems, <i>n</i> (%)	110 (5.1)
Hearing problems, <i>n</i> (%)	297 (13.8)
Chronic pain, <i>n</i> (%)	46 (2.1)
Chronic illness, <i>n</i> (%)	497 (23.1)
Alcohol consumption, <i>n</i> (%)	
$\geq 5$ days per week	609 (28.4)
1–4 days per week	914 (42.6)
Once or twice a month	257 (12.0)
Every couple of months or less	368 (17.1)
Social isolation score (0–9), mean (s.d.)	4.8 (1.8)
Engaged in civic activities, <i>n</i> (%)	399 (18.6)
Have a hobby, <i>n</i> (%)	1768 (82.3)
Read a daily newspaper, <i>n</i> (%)	1448 (67.4)
Frequency of cultural engagement	
Never	216 (10.1)
Less than once a year	324 (15.1)
Once or twice a year	584 (27.2)
Every few months	635 (29.6)
Once a month or more	389 (18.1)
Number of participants with depression across the 10 years, <i>n</i> (%)	616 (28.7)

adjusting just for sociodemographic factors, but results were attenuated when considering other health and social covariates.

### Sensitivity analyses

Our sensitivity analysis found very similar results when weighting to account for missing data (using fully adjusted models: for every few months,  $OR = 0.71$ , 95% CI 0.48–1.05; for once a month or more,  $OR = 0.53$ , 95% CI 0.34–0.83) (supplementary Table 1).

When we took into account subclinical symptoms of depression at baseline through exclusions of participants feeling depressed over the previous week or participants with an indication of subclinical CES-D symptoms at baseline, results were materially unaffected (supplementary Table 2).

To test the reverse causal hypothesis of depressive symptoms leading to reduced engagement with culture, we re-ran the regression models excluding the 174 participants who showed above-threshold symptoms of depression in the first wave following baseline. This exclusion had little effect on the estimates (using fully adjusted

**Table 2** Depression incidence rates per 100 person-years and 95% confidence intervals by frequency of cultural engagement

	New cases of depression in participants over the 10 years, <i>n</i>	Rate per 100 person-years (95% CI)
Never	89	5.17 (4.20–6.37)
Less than once a year	104	3.80 (3.14–4.61)
Once or twice a year	174	3.47 (2.99–4.03)
Every few months	167	2.99 (2.57–3.48)
Once a month or more	82	2.31 (1.86–2.87)

**Table 3** Associations between cultural engagement and the risk of developing depression over the following 10 years ( $n = 2148$ )<sup>a</sup>

	Model 1			Model 2			Model 3		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Never		Reference			Reference			Reference	
Less than once a year	0.77	0.53–1.13	0.19	0.80	0.54–1.18	0.26	0.80	0.54–1.19	0.27
Once or twice a year	0.71	0.50–1.01	0.060	0.75	0.52–1.07	0.10	0.74	0.51–1.06	0.10
Every few months	<b>0.65</b>	<b>0.45–0.93</b>	<b>0.018</b>	<b>0.69</b>	<b>0.48–1.00</b>	<b>0.048</b>	<b>0.68</b>	<b>0.47–0.99</b>	<b>0.046</b>
Once a month or more	<b>0.49</b>	<b>0.32–0.73</b>	<b>0.001</b>	<b>0.52</b>	<b>0.34–0.79</b>	<b>0.002</b>	<b>0.52</b>	<b>0.34–0.80</b>	<b>0.003</b>

Results in bold are significant.

a. Model 1 adjusted for baseline depressive symptoms, age, gender, marital status, ethnicity, educational attainment, employment status and wealth. Model 2 additionally adjusted for eyesight, hearing, chronic health conditions, pain and alcohol consumption. Model 3 additionally adjusted for social networks, civic engagement, having a hobby or pastime, or reading a daily newspaper.

models: for every few months, OR = 0.67, 95% CI 0.44–1.02; for once a month or more, OR = 0.58, 95% CI 0.36–0.93; supplementary Table 3).

Including participants who already showed depressive symptoms at baseline also did not lead to results being attenuated (using fully adjusted models: for every few months, OR = 0.66, 95% CI 0.47–0.94; for once a month or more, OR = 0.57, 95% CI 0.38–0.84; supplementary Table 4).

Using the alternative cut-off score of  $\geq 4$  on CES-D, again results were materially unaffected, although there was a slight loss of power because only 419 participants with depression were detected over the 10 years compared with 616 using the lower threshold (using fully adjusted models: for every few months, OR = 0.67, 95% CI 0.44–1.01; for once a month or more, OR = 0.58, 95% CI 0.37–0.94; supplementary Table 5).

Finally, results were maintained even when adjusting for open personality type (cultural engagement once a month or more, OR = 0.53, 95% CI 0.34–0.82; supplementary Table 6).

## Discussion

### Main findings

The main finding of this study was a dose-response relationship between frequency of cultural engagement and the risk of developing depression over a 10-year period among adults aged  $\geq 50$  who were free from depression at baseline. Notably, this finding was independent of sociodemographic factors, health and behavioural factors and other forms of social and civic engagement including other hobbies, social interactions, community group and civic engagement. It was also independent of open personality type.

### Comparisons with findings from other studies

In relation to prior research, this is the first known longitudinal study to explore cultural engagement in relation to the prevention of depression in older age. One previous cross-sectional study found associations between receptive cultural engagement and both low anxiety and low depression (using the Hospital Anxiety and Depression Scale) as well as good satisfaction with life (using a single self-report item).<sup>28</sup> However, as this study was cross-sectional, it is unclear whether reverse causality was present.

Other cross-sectional studies have, in contrast, found no association between cultural engagement and feelings of anxiety and depression (using the EuroQol-5D).<sup>29</sup> Two previous longitudinal studies have explored mental health more broadly. A Swedish occupational cohort found weak associations between receptive cultural engagement in the workplace and emotional exhaustion (using the Maslach Burnout Inventory) but not depression symptoms (using the Hopkins Symptom Checklist).<sup>30</sup> And a Swiss household study found no associations between receptive cultural engagement and either common somatic symptoms (using a cumulative scale similar

to the Patient Health Questionnaire) or prevalence of low mood or general life satisfaction (both using a single self-report item).<sup>31</sup> These studies are also set in the context of others that have found associations between receptive cultural engagement and well-being and life satisfaction.<sup>32</sup> However, our study is the first to focus specifically on the prevention of depression in older age (rather than the presence of general mental health symptomatology) using a longitudinal sample and a validated depression scale.

### Strengths and limitations

The strengths of this study are that it used well-validated measures of depression and tested different thresholds, finding consistent results. It also used data from a large nationally representative cohort study with consistent collection of key variables every 2 years and a follow-up of a decade. The rich data-set enabled us to include all identified confounding variables in our statistical models.

The main limitation is that this study is observational rather than interventional. We have presented longitudinal associations that attempt to account for issues such as reverse causality and confounding. But causality cannot be assumed and it is possible that residual variables remain. Consequently, interventional studies are recommended as a way of exploring whether cultural engagement could be recommended as an activity to promote positive mental health in older adults and reduce the incidence rate of depression in older adults; especially those identified as being most at risk. Indeed, there have already been calls for more use to be made of cultural venues such as museums and galleries as sites for health promotion and public health interventions,<sup>30</sup> and these results suggest there could be benefits for mental health.

A further limitation is that it is possible that subthreshold low mood or depression may have contributed to reduced cultural engagement. However, we ran analyses with and without participants with depression at baseline, as well as further excluding participants who had taken antidepressants or had counselling in the past 2 years, who had even very minor symptoms of depression at baseline, who reported feeling low over the past week even if they did not score above-threshold at baseline and who went on to develop depression within 2 years of baseline. None of these additional analyses affected the significance of our results.

Finally, it is possible that a participant experienced a depressive episode in between waves but did not report it to their doctor and recovered by the next CES-D assessment. However, this is anticipated to be a very low number of participants and given the robustness of our findings in response to a range of sensitivity analyses we do not believe this would have affected the broad findings reported here.

### Summary

In conclusion, we found that engagement with cultural activities (including going to the cinema, museums or galleries or the theatre, concert or opera) appears to be an independent risk-reducing factor

for the development of depression in older age. Given our analyses specifically tested the potential contribution of reverse causality but found no change in results, this association may be ascribed to multiple components of cultural engagement including social interaction, mental creativity, cognitive stimulation and gentle physical activity.

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## Supplementary material

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