PHYSICAL ACTIVITY MODIFIES THE ASSOCIATION BETWEEN

DEPRESSION AND COGNITIVE FUNCTION IN OLDER ADULTS

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ABSTRACT

Objective: To examine the effects of gender and physical activity on the interplay between depression and cognitive function in late adulthood.

Method: Data on physical activity, depressive symptoms, two measures of cognitive function (the Animal Fluency Test (AFT) and the Digital Symbol Substitution Test (DSST)), and other demographic characteristics were extracted from 2,604 adults aged ≥ 60 years participating in the National Health and Nutrition Examination Survey (2011-2014). Gender-specific multiple linear regressions examined the relationship between depressive symptoms and cognitive function in the overall sample and stratified by level of leisure-time physical activity.

Results: Sample included 1327 women and 1277 men (mean age 69.0 years), Women with moderate to severe depressive symptoms had a 1.7 (95% CI: 0.5 to 2.9) point lower score on the *AFT* than those with none or minimal depressive symptoms. No such association was observed in men. In the stratified analyses, lower *AFT* test scores only persisted among women who were inactive. With respective to the *DSST*, lower test scores were observed in in both men (-7.2, 95% CI: -13.1 to -1.3) and women (-6.4, 95% CI: -11.8 to -1.1) with moderate to severe depressive symptoms. In the stratified analyses, this association persisted in those who were insufficiently active, but attenuated to null among those engaged in sufficient physical activity.

Conclusions: Moderate-to-vigorous physical activity modifies the depression-cognition relationship and preserves cognition function. Engaging in sufficient (150 min/week) leisure-time physical activity at moderate-to-vigorous intensity may protect those with depressive symptoms from cognitive decline in older age.

INTRODUCTION

Depression is a prevalent mental health problem among older adults (Luppa et al., 2012). Depressive episodes are linked with various aspects of cognitive function, including memory (Burt et al., 1995; Kindermann and Brown, 1997), perceptual speed (Bielak et al., 2011), information processing (Shilyansky et al., 2016) and executive function (Snyder, 2013). Moreover, evidence also suggests that individuals with depression suffer persistent and global cognitive impairment (Ganguli et al., 2006; Reppermund et al., 2007) and are at increased risk of developing Alzheimer's disease (Sierksma et al., 2010). Epidemiological data suggested that depression and cognitive impairment are more frequently reported in females than males among older adults   (Bonsang et al., 2017; Piccinelli and Wilkinson, 2000).

In light of the considerable health consequences of depression and cognitive impairment and the consistent link between these two factors, researchers have long been interested in identifying factors that may help to prevent depression and cognitive decline during the process of aging. Antidepressants are commonly used for treating depression, and one would posit the depression-reducing treatment might also lead to cognitive benefits. However, approximately 30% of individuals with depression are not responsive to antidepressants (Baldessarini, 1989), and inconsistent findings have been reported on whether successful antidepressant treatment improves cognition. Until recently, a large-scale randomized longitudinal study found none of three commonly used antidepressants were efficacious in buffering cognitive impairments (Shilyansky et al., 2016).

Hence, researchers and health practitioners are interested in seeking modifiable variables (e.g., psychological and behavioural factors) that may protect older adults from cognitive deficits and /or depressive symptoms. Such variables could serve as a basis for designing and implementing behavioural interventions. Physical activity is a non-invasive, relatively low-risk and low-cost behavioural modality, and it has consistently been found to be beneficial for both depression (Bridle et al., 2012; Josefsson et al., 2014; Schuch et al., 2016) and cognitive function (Blondell et al., 2014; Carvalho et al., 2014) among older adults. Notably, the anti-depressant effect of physical activity has been found to be comparable with drug treatments (Blumenthal et al., 1999). Thus far, there has been no prior study investigating whether physical activity may also prevent cognitive decline among those with depressive symptoms.

Therefore, we sought to address this knowledge gap using a population-based dataset to: 1) examine the association between depression and cognitive function among older adults, and 2) establish whether the depression-cognition relationship is influenced by sex and/or physical activity. In particular, we were interested in whether physical activity modifies the relationship between depression and cognitive function. Based on the published literature, we postulated that depression would be associated with cognitive function among older adults, and the pattern of depression-cognition relationship would vary as a function of gender and physical activity.

MATERIAL AND METHODS

Study Population

The National Health and Nutrition Examination Survey (NHANES) was designed to provide cross-sectional estimates on the prevalence of health, nutrition, and potential risk factors among the civilian non-institutionalized U.S. population up to 85 years of age (Centres for Disease Control and Prevention, 2016). In brief, NHANES surveys a nationally representative complex, stratified, multistage, probability clustered sample of about 5,000 participants each year in 15 counties across the country. Survey participants were asked to attend physical examination at a mobile examination center (MEC). The NHANES obtained approval from the National Center for Health Statistics Research Ethics Review Board and all participants provided written consent. We extracted and aggregated data on cognitive function, depressive symptoms, physical activity, and other characteristics from NHANES in 2011 to 2012, and 2013 to 2014. Cognitive functioning tests were only administered to adults aged 60 years and older, which subsequently restricted our sample to older adults.

Cognitive Functioning Tests

Data on two cognitive function tests, the Animal Fluency Test (AFT) and the Digital Symbol Substitution Test (DSST), were extracted. Both tests have been widely used in large-scale screenings, epidemiological and clinical studies (Plassman et al., 2007; Proust-Lima et al., 2007; Tuokko et al., 2017). For each test, cognitive function was evaluated by a score that summarizes the total number of correct answers within a given time period. The *AFT* examines categorical verbal fluency, which is a component of executive function. It asks participants to name as many animals as possible in one minute, with the total number of named animals summarized as the

test score. The *DSST* is a performance module from the Wechsler Adult Intelligence Scale (WAIS III), assessing processing speed, sustained attention and working memory (Chen et al., 2017). The task in the *DSST* provides each participant a paper form that has a key at the top containing 9 numbers paired with symbols. Participants are asked to copy the corresponding symbols in the 133 boxes that adjoin the numbers in two minutes, with the total number of correct matches summarized as the test score.

Depressive symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9), a validated 9-item depression screener that asks about the frequency of symptoms of depression over the past 2 weeks (Kroenke et al., 2001). Each item was scored on a 0-3 scale, with a total score ranging from 0 to 27. PHQ-9 scores categorise depression severity as "none or minimum" (0-4), "mild" (5-9), "moderate" (10-14), "moderately severe" (15-19), and "severe" (20-27). For current analyses, participants who scored 10 or more were combined into one group as *clinically relevant* depression, as such a diagnosis has shown a sensitivity of 88 % and a specificity of 88 % for major depression (Kroenke et al., 2001; Manea et al., 2012).

Self-reported leisure-time physical activity

Participants self-reported their activity patterns using questions based on the Global Physical Activity Questionnaire (GPAQ) (Hallal et al., 2012). Levels of leisure-time physical activity were calculated as the minutes per week that participants reported engaging in moderate-to-vigorous-intensity physical activity. Participants reported the frequency and duration of physical activity in a typical week, at vigorous and moderate intensities, respectively. We summarized the total number of minutes for physical activity in each intensity, where the number of minutes spent in

vigorous-intensity physical activity were doubled and added to the number of minutes of moderate-intensity physical activity to approximately match the metabolic equivalent of task value (Zhao et al., 2014). Older adults were classified as inactive (zero min/week moderate-to-vigorous physical activity), insufficiently active (<150 min/week moderate-to-vigorous physical activity), and sufficiently active (≥150 min/week moderate-to-vigorous physical activity) based on physical activity guidelines (World Health Organization (WHO), 2018).

Socio-demographic characteristics

Data on age, sex, race and ethnicity, education and smoking status were extracted. Based on self-reported race and ethnicity, participants were classified into one of the three racial/ethnic groups: Non-Hispanic White, Non-Hispanic Black, and Hispanic and others. Participant's education levels were classified into four groups: less than high school, high school, some college, and college graduate or above. Marital status was summarized into two groups: live with someone (married, and living with partner) and live alone (widowed, divorced, separated, never married). Finally, we classified participants into three smoking groups: never smokers (did not smoke 100 cigarettes in life and do not smoke now), former smokers (smoked 100 cigarettes in life and do not smoke now), and current smokers (smoked 100 cigarettes in life and smoke now). Weight and height were measured at the time of physical examination at the MEC. The measurements followed standard procedures and were carried out by trained technicians using standardized equipment. BMI was calculated as weight in kg/(height in meters)^2. We categorized study participants into standard BMI categories: underweight (<18.5kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30.0 kg/m^2) (World Health Organization,

2000). For analytic purposes, we combined underweight and normal weight (<25 kg/m^2).

<u>Chronic illness</u>

We included four chronic conditions: cardiovascular diseases, diabetes, cancer and arthritis. Participants were considered as having chronic illness if they self-reported ever having been told by a physician that they have the following conditions: congestive heart failure, coronary heart disease, heart attack, a stroke, diabetes, cancer, or arthritis.

Statistical Analysis

Survey analysis procedures were used to account for the sample weights (MEC exam weight), stratification, and clustering of the complex sampling design to ensure nationally representative estimates. NHANES adults aged 60 years and older with completed information on cognitive functioning, depressive symptoms, and other characteristics were included in the analyses. Descriptive characteristics were analysed separately in men and women, due to the documented gender difference in depression (Piccinelli and Wilkinson, 2000) and cognitive function during later-life (Bonsang et al., 2017). We summarized weighted means and standard errors for continuous variables, weighted proportions for categorical variables, and provided explorative *p*-values for gender comparison.

Gender-specific multiple linear regressions were carried out to quantify associations between levels of severity in self-reported depressive symptoms and cognitive function test scores. The multivariable models were adjusted for age, race and ethnicity, BMI, education level, smoking status, level of leisure-time physical activity, and chronic conditions. To explore the effect modification role of physical activity to

8

inform potential behaviour interventions, we stratified the analyses by leisure-time

physical activity categories and estimated the linear associations of depressive

symptom severity and cognitive test scores in each leisure-time physical activity

strata. We examined the normality of residuals using kernel density estimate and

standardized normal probability plots for all the linear regression models. Finally, we

estimated the marginal means in multivariable adjusted generalized linear models for

each modelled outcome of cognitive test scores. All statistical significance was set at

$p<0.05$. All statistical analyses were performed using STATA version 14.0 (STATA

Corp., Texas, USA).

RESULTS

There were 2,604 adults aged ≥ 60 years in the two NHANES waves who with complete data on cognitive functioning tests and depressive symptoms. Participants' mean age was 69.0 years at the time of examination, and their mean BMI was 29.1 kg/m^2. We observed statistically significant gender differences in most characteristics, except for age and race/ethnicity (Table 1). Compared with women, a greater proportion of men were overweight (BMI ≥ 25.0 kg/m^2), were educated to degree level or higher, lived with someone and were former or current smokers, and fewer had chronic conditions. Men were also more likely than women to be sufficiently active and have none or minimal depressive symptoms, but had lower cognitive function.

Tables 2 and 3 summarize both the age-adjusted and multivariable-adjusted associations between the severity of depressive symptoms and cognitive functioning test scores in linear regression models, for men and women respectively. Relative to women with none or minimal depressive symptoms, women with moderate to severe depressive symptoms had a 1.7 (95% CI: 0.5 to 2.9) point lower score on the *AFT* test. No such association was observed in men. When we stratified the models by leisure-time physical activity, the lower *AFT* test score in women only persisted among those who were inactive. Among those who were active (sufficiently or insufficiently), there was no difference in *AFT* test performance between women who experienced moderate to severe depressive symptoms than those with none or minimal depressive symptoms.

With respect to cognitive function assessed by the *DSST*, relative to older adults with none or minimal depressive symptoms, women with moderate to severe depressive

symptoms had a 5.4 (95% CI: 1.0 to 9.9) point lower score, and men with moderate to severe depressive symptoms had a -5.6 (95% CI: -11.5 to 0.2) point lower score which was borderline significant. The poorer cognitive test performance assessed by the *DSST* in those with moderate to severe depressive symptoms persisted in both inactive men (-7.2, 95% CI: -13.1 to -1.3) and inactive women (-6.4, 95% CI: -11.8 to -1.1), and women who were only insufficiently active (-7.3 95% CI: -12.4 to -2.1), yet attenuated to null among those who were engaging in sufficient physical activity.

DISCUSSION

In a nationally representative sample of US older adults, we found that moderate to severe depressive symptoms were associated with poorer cognitive function and in women more so than in men. Importantly, physical activity, as a viable behavioural modality, was found to modify the depression-cognition relationship, with cognitive function preserved among older adults with moderate to severe depression symptoms who were sufficiently active.

Our finding that older adults with moderate to severe depressive symptom tended to score lower on cognitive tests is consistent with previous studies demonstrating an inverse association between depressive symptoms and cognitive function among the elderly using Australian and French study samples (Bielak et al., 2011; Paterniti et al., 2002). In addition, our analyses indicate that the inverse correlation between depressive symptoms and cognitive function exist predominantly among older women.

Many studies have sought to explore gender differences in depression and cognitive function, with inconsistent findings (Barrett-Connor and Kritz-Silverstein, 1999; Djernes, 2006; Forlani et al., 2014; Lin et al., 2015). However, little attention has been given to whether gender influences the pattern of the association between these two variables. A previous study suggested that depressed women performed significantly worse compared to depressed men in tests of visuospatial recall and cognitive interference (Sárosi et al., 2008). It was inferred that the pattern of association between depression and cognitive function in older adults could be gender-specific. Our study adds empirical evidence to suggest that older women who suffer from depression may be more vulnerable than older men to cognitive decline.

12

Such results warrant future replication and highlight the need to seek effective measures to reduce depressive and cognitive deterioration among older adults, especially older women.

Depression is common among older adults, with prevalence estimates ranging from 4.6 to 9.3% (Luppa et al., 2012). In the current study, 5.1% of men and 8.3% of women experienced moderate to severe depressive symptoms; a threshold for clinical relevance. Compelling research evidence has shown that physical activity is an efficacious treatment for late-life depression (Schuch et al., 2016; Silveira et al., 2013; Stathopoulou et al., 2006), and that physical activity may offer comparable benefits to antidepressant medication (Blumenthal et al., 1999). Given that antidepressants are associated with a number of undesirable side effects (Alexopoulos, 2011; Coupland et al., 2011), encouraging older individuals with depression to embrace physical activity may be a promising non-invasive and efficacious method of combating depressive symptoms.

One major drawback of previous studies on the clinical effectiveness of physical activity was separating depression and cognitive function, without considering the role of physical activity in the dynamics of depression and cognitive decline in late life. This is striking given that a bulk of evidence has shown that later-life depression and cognitive impairments are inter-correlated, and the reciprocal relationship, as many have posited, awaits clarification. Most studies tend to suggest that depression may act as an important cause of cognitive decline, whereas an accumulation of recent evidence suggests that the relationship may be bi-directional (Yang et al., 2017).The relationship between depression and cognition appears to be complex. Understanding factors that modify/mediate the depression-cognition relationship should help identify strategies of coping with them.

The current study examined the role of physical activity in the interplay between depression and cognitive function. Although individuals with depressive symptoms were more likely to score poorly on cognitive tests, this inverse association was rendered non-significant as a function of engaging in sufficient amount of leisure-time physical activity at moderate to vigorous intensity. Specifically, inferior performance in tests of verbal fluency and processing speed, as well as sustained attention and working memory was observed among those with moderate to severe depression, but not in those who engaged in a physically active lifestyle.

As noted above, participation in physical activity exerts a protective effect on mood and cognition in late adulthood, with at least a moderate intensity required to maximize such benefits. To our knowledge, the current study is the first to explore whether the depression-cognition relationship varies as a function of exercise, and thus addresses an important gap in the literature. Our findings deliver a clear message that those who suffer moderate to severe depressive symptoms are at greater risk for cognitive deterioration, but engaging in more than 150 min/week leisure time physical activity at moderate-to-vigorous intensity has the potential to protect those with depressive symptoms from cognitive decline. Findings of the current study are both seminal and encouraging from the perspective of health promotion. Cognitive function is essential to one's ability to maintain a healthy lifestyle (e.g, regular physical activity). Based on 177 older adults who participated in a 12-month exercise trial examining exercise effects on brain structure and function, McAuley and Colleagues (2011) found that higher levels of executive function and use of self-regulatory strategies at the beginning of the exercise program enhanced exercise self-efficacy, which in turn leads to greater exercise adherence. This is unsurprising that executive function, as a higher and meta-level cognitive processes, is essential to

guiding and managing purposeful and goal-directed behaviors, especially in no-routine circumstances (Etnier & Chang, 2009). Taken together the prospective evidence of inverse bidirectional association between physical activity and general depressive symptoms (Stavrakakis et al., 2012), it is plausible that physical activity can prevent cognitive impairment among older adults who suffer depressive symptoms, and the preservation/enhancement of cognitive function may in turn help them better keep physically active and gain the anti-depressant benefits from physical activity participation. Given that depressive symptoms in older adults are often accompanied by sustained cognitive impairment that are often left untreated with antidepressants (Shilyansky et al., 2016), our results lend support for health practitioner and policy-makers to promote physical activity of moderate and vigorous intensity, especially for those have demonstrated signs of marked depressive symptoms.

Strengths of the current study include using a large, nationally representative sample of the US population, and testing the modifying effect of physical activity on the depression-cognition relationship using two different cognitive tests. However, one must also take into consideration several limitations of our study. First, the cross-sectional nature of the current study excludes the possibility of examining the causal relationship. Exercise intervention has been consistently found to benefit depression and cognitive function, but there is a lack of explorations on the interactive effects of exercise on these two inter-correlated outcomes. Future studies are encouraged to design exercise interventions to fill this research gap. Along this line, a number of issues should be factored into the study design. Cognitive function in patients with recurrent depression has been found to decline with each successive episode of depression (Basso and Bornstein, 1999; Stordal et al., 2004), and cognitive

functioning continues to decline long after the remission of depressive episodes (Airaksinen et al., 2006). The effects of depression on cognitive function are likely to be pervasive and long-lasting. However, our study is limited in that the measure of depression did not differentiate those in different stages of depression (i.e., remission vs. recurrent). The dynamic influence of exercise on depression and cognitive function is certainly worth exploring in a longitudinal and experimental manner. This is particularly intriguing given that the reciprocal relationship not only exists between depression and cognition (Yang et al., 2017), but has also been observed between physical activity and depression (Stavrakakis et al., 2012; Steinmo et al., 2014), and physical activity and executive function (Daly et al., 2015).

Second, cognitive function is a broad term including various aspects of how individuals obtain, process and preserve information. Various cognitive components may be related to depression in different manners. To date, most evidence points to the link between depressive symptoms and memory (Burt et al., 1995), perceptual speed (Bielak et al., 2011), attention and attentional shifting (Harmer et al., 2002; Ravnkilde et al., 2010), information processing (Shilyansky et al., 2016), visuo-spatial processing and psychomotor function (Mondal et al., 2007), and executive function (Snyder, 2013). The depression-cognition relationship is complicated by the severity of depression and cognitive declines. Most robust evidence has been derived from individuals with clinical major depression (Bora et al., 2013) or cognitive deficits such as dementia and Alzheimer's Disease (Yang et al., 2017). The current research is a population-based study that included two cognitive tests which only allow us to tap into limited aspects of cognitive function. In addition, we were unable to identify clinical samples as we did not employ standardized diagnostic tools of depressive and/or cognitive conditions.

The findings of our study support the position that depressive symptoms are associated with potential cognitive function decline, and that engagement in physical activity can help to preserve cognitive function among those with moderate to severe depression. The findings can not only serve as the basis for developing and implementing physical activity interventions, but also help to better advise the public to protect people against cognitive decline and depression as we age.

Acknowledgement

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Table 1. Socio-demographic Characteristics of Adults Aged 60 Years or Older from the NHANES (2011-2014), by Gender

		Men	Women	P-values
	N	1277	1327	
	Weighted N	22,621,827	26,368,166	
Age (years)	Mean (s.e.)	68.7 (0.3)	69.3 (0.3)	0.110
BMI (kg/m2)				0.004
<18.5	%	0.9	1.7	
18.5 – 24.9	%	22.3	27.4	
25.0 – 29.9	%	40.8	31.4	
≥ 30	%	36.0	39.5	
Race				0.221
Non-Hispanic White	%	81.2	80.0	
Non-Hispanic Black	%	7.1	8.8	
Hispanic and Other	%	11.7	11.2	
Education				<.001
Less than 12th grade	%	15.0	15.3	
High School	%	19.2	24.1	
Some college	%	28.5	34.6	
College graduate or above	%	37.4	26.0	
Marital status				<.001
Live with someone	%	79.1	53.8	
Live alone	%	20.9	46.2	
Smoking				<.001
Never smoker	%	39.6	58.1	
Former smoker	%	48.1	32.3	
Current smoker	%	12.3	9.6	
Chronic conditions				0.022
Yes	%	65.9	71.3	
No	%	34.1	28.7	
Leisure time physical activity (LTPA)				0.015
Inactive	%	51.2	55.5	
Insufficiently Active	%	14.8	16.4	
Sufficiently Active	%	34.0	28.1	
Depressive symptoms				<.001
None or minimum	%	85.1	74.6	
Mild	%	9.8	17.1	
Clinically relevant	%	5.1	8.3	

Table 2. Associations between Depression and The Animal Fluency Test score from Unadjusted and Multivariable Linear Regression Models among Adults Aged 60 Years or Older from the NHANES (2011-2014).

Depressive symptomsc	Age adjusted Beta-coefficient (95% CI)a		Adjusted Beta-coefficient (95% CI)b		Marginal mean	Age adjusted Beta-coefficient (95% CI)a	Adjusted Beta-coefficient (95% CI)b	Marginal mean
Overall								
Men (n=1277)						Women (n=1327)		
None or minimum	Reference		Reference		18.7	Reference	Reference	18.2
Mild	-1.4	(-2.8 to 0.0)	-0.7	(-1.9 to 0.4)	18.0	-0.8 (-1.9 to 0.4)	-0.2 (-1.2 to 0.7)	18.0
Moderate to severe	-2.1	(-3.8 to -0.3)	-0.7	(-2.7 to 1.3)	18.0	-3.2 (-4.4 to -2.0)	-1.7 (-2.9 to -0.5)	16.5
Inactive								
Men (n=703)						Women (n=777)		
None or minimum	Reference		Reference		17.6	Reference	Reference	17.2
Mild	-0.5 (-2.4 to 1.4)		-0.4 (-1.8 to 1.0)		17.2	0.0 (-1.1 to 1.2)	0.4 (-0.7 to 1.4)	17.5
Moderate to severe	-1.5 (-2.9 to -0.1)		-0.9 (-2.6 to 0.7)		16.6	-2.9 (-4.6 to -1.3)	-2.2 (-3.5 to -0.8)	15.0
Insufficiently active								
Men (n=194)						Women (n=225)		
None or minimum	Reference		Reference		19.3	Reference	Reference	18.0
Mild	-1.8 (-5.8 to 2.2)		-1.4 (-5.1 to 2.4)		17.9	-0.6 (-1.5 to 0.4)	-0.5 (-1.6 to 0.6)	17.5
Moderate to severe	-1.3 (-8.0 to 5.4)		-0.7 (-9.3 to 7.9)		18.6	-2.0 (-5.2 to 1.3)	-0.2 (-3.8 to 3.5)	17.8
Sufficiently active								
Men (n=380)						Women (n=325)		
None or minimum	Reference		Reference		20.1	Reference	Reference	20.4
Mild	-2.0 (-3.7 to -0.3)		-0.7 (-2.6 to 1.1)		19.3	-1.9 (-4.6 to 0.8)	-1.9 (-4.8 to 1.1)	18.5
Moderate to severe	-0.6 (-5.9 to 4.7)		1.4 (-4.6 to 7.5)		21.5	-2.1 (-5.0 to 0.7)	-0.6 (-3.0 to 1.7)	19.7

a Adjusted for age; b Adjusted for age, BMI, race and ethnicity, education, marital status, smoking status, and chronic illness (cardiovascular diseases, diabetes, cancer and arthritis); c Patient Health Questionnaire (PHQ-9): None or minimum (0-4) Mild (5-9) Moderate to severe (10-27)

Table 3. Associations between Depression and the Digital Symbol Substituion Test score from Unadjusted and Multivariable Linear Regression Models among Adults Aged 60 Years or Older from the NHANES (2011-2014).

Depressive symptomsc	Age adjusted Beta-coefficient (95% CI)a	Adjusted Beta-coefficient (95% CI)b	Marginal mean	Age adjusted Beta-coefficient (95% CI)a	Adjusted Beta-coefficient (95% CI)b	Marginal mean
Overall						
	Men (n=1277)			Women (n=1327)		
None or minimum	Reference	Reference	51.4	Reference	Reference	55.8
Mild	-5.2 (-8.4 to -1.9)	-2.9 (-5.2 to -0.6)	48.5	-5.9 (-9.0 to -2.7)	-4.2 (-6.6 to -1.8)	51.6
Moderate to severe	-10.3 (-17.4 to -3.2)	-5.6 (-11.5 to 0.2)	45.8	-10.9 (-15.6 to -6.3)	-5.4 (-9.9 to -1.0)	50.4
Inactive						
	Men (n=703)			Women (n=777)		
None or minimum	Reference	Reference	48.6	Reference	Reference	52.9
Mild	-4.7 (-9.9 to 0.4)	-4.4 (-7.9 to -0.9)	44.2	-4.6 (-8.8 to -0.5)	-4.0 (-7.4 to -0.5)	48.9
Moderate to severe	-9.3 (-16.0 to -2.5)	-7.2 (-13.1 to -1.3)	41.3	-10.3 (-15.7 to -4.8)	-6.4 (-11.8 to -1.1)	46.5
Insufficient active						
	Men (n=194)			Women (n=225)		
None or minimum	Reference	Reference	52.9	Reference	Reference	57.5
Mild	-4.8 (-10.5 to 1.0)	-3.3 (-6.7 to 0.1)	49.7	-5.5 (-12.2 to 1.1)	-3.7 (-9.6 to 2.3)	53.9
Moderate to severe	-6.7 (-18.5 to 5.1)	-1.8 (-10.4 to 6.8)	51.1	-13.2 (-21.5 to -4.9)	-7.3 (-12.4 to -2.1)	50.3
Sufficient active						
	Men (n=380)			Women (n=325)		
None or minimum	Reference	Reference	55.0	Reference	Reference	60.3
Mild	-3.5 (-8.4 to 1.3)	0.3 (-3.8 to 4.4)	55.3	-6.3 (-11.8 to -0.8)	-4.4 (-9.9 to 1.1)	56.0
Moderate to severe	-5.9 (-23.7 to 11.9)	1.3 (-16.3 to 18.8)	56.3	-4.5 (-17.1 to 8.2)	1.3 (-8.6 to 11.3)	61.7

a Adjusted for age; b Adjusted for age, BMI, race and ethnicity, education, marital status, smoking status, and chronic illness (cardiovascular diseases, diabetes, cancer and arthritis); c Patient Health Questionnaire (PHQ-9): None or minimum (0-4) Mild (5-9) Moderate to severe (10-27)