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Does Late-Life Depression Counteract the Beneficial Effect of Physical Activity on Cognitive Decline? Results From the NESDO Study

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Abstract

Objectives: Depression both affects physical activity (PA) and cognition in older persons, yet its impact on the association between PA and cognitive decline is to be determined. We aimed to investigate the association between baseline PA and cognitive functioning over time, stratified for depression. **Methods:** We used data of the Netherlands Study of Depression in Older persons (NESDO), a multi-site cohort study with 6-years follow-up. Patients with complete data on PA and cognitive functioning at baseline were included, yielding 394 participants for the analyses of whom 297 were depressed and 97 non-depressed. PA (continuous) was measured with the International Physical Activity Questionnaire. Linear mixed models were used to determine differential effects of baseline PA on the rate of decline of 5 standardized outcomes of cognitive functioning over 6-year follow-up. For this purpose, we examined the significance of the interaction-term (PA*time) in both basic and adjusted models. We also assessed the association between time and cognitive functioning. All analyses were stratified for depression. **Results:** In both groups, no robust significant interactions of PA with time were found. Furthermore, only decline in working memory was significantly worse in the depressed compared to the non-depressed. **Conclusion:** At older age, the impact of a more inactive lifestyle on cognitive decline was shown to be limited, irrespective of depression that appeared to worsen age-related decline of working memory only. As a higher PA-level at older age has a positive effect on a multitude of other health outcomes, PA should still be encouraged in this population.

Keywords

physical activity, long-term cognitive functioning, depression, older persons

Introduction

As the population ages, new challenges arise, such as how to gain an extended period of good health with increasing longevity.[1] Healthy aging is closely linked to the preservation of cognitive capabilities.[2] Physical activity (PA) may be employed as a potential protective strategy for healthy aging in general, and for cognitive decline in particular.[3] PA may slow cognitive decline directly through increased blood flow resulting in preservation of the cardiovascular integrity of the brain,[4] or indirectly by reducing other risk factors (namely, cardiovascular disease, obesity, and diabetes).[5] Two meta-analyses examining prospective cohort studies including persons over 40[6] and 65 years[7] demonstrated clear evidence for an association between higher levels of (PA) and a reduced risk of cognitive decline and (Alzheimer's) dementia.[6,7]

Besides the aforementioned somatic conditions, depression has also been identified as a risk-factor of cognitive decline, especially in old age.[8,9] Underlying pathophysiological mechanisms have not yet been fully elucidated, however several hypotheses have been formulated.[10] For example, both dementia and depression may share the same pathophysiology as they both have been associated with vascular disease, hippocampal atrophy, increased deposition of amyloid-β plaques,

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low-grade inflammatory changes, and deficits of nerve growth factors.[11] Next, it has also been hypothesized that depression and behavioral changes seen in depression (among others reduced PA) may lead to immune system dysregulation that may contribute to pathological brain aging and cognitive decline.[10]

In older depressed persons, PA may be beneficial as it may positively influence both mood and cognition.[12] Two cross-sectional studies demonstrated a mediating role of depressive symptoms in the association between self-reported PA and cognitive decline in older persons, indicating that PA results in preserved cognitive functioning via reduction of depressive symptomatology.[13,14] Vice versa, it is plausible that the presence of depression counteracts the protective effect of higher levels of PA on long-term cognitive functioning since, as previously mentioned, depression has been associated with pathological brain aging. However, studies focusing on this counteracting effect are lacking.

Therefore, we aimed to investigate the association of levels of self-reported PA at baseline and cognitive functioning during 6-yrs follow-up in older persons without dementia, stratified for depression. We expected higher levels of PA to be associated with a slower cognitive decline, especially in the non-depressed group compared to the depressed group. Further insight in the role of late-life depression on the association between PA and cognitive decline is of interest as it may help clinicians to apply tailor-made interventions to postpone cognitive decline in older persons.

Methods

Study Sample

Data were available from participants of the Netherlands Study of Depression in Older persons (NESDO), a longitudinal, multisite, naturalistic cohort study that included 378 older adults with a depressive disorder and 132 non-depressed older adults with no diagnosis of depression during their lifetime (comparison group). The cohort of depressed older people was sourced from both specialized mental health services and general practitioners, in 5 regions throughout the Netherlands. All participants were aged 60 years and older and were included between 2007 through 2010. Late-life depression at various developmental and severity stages was included through this inclusion process. Exclusion criteria were a diagnosis of dementia or a suspected dementia according to the clinician, baseline Mini Mental State Examination (MMSE) score <18, another primary severe psychiatric disorder or insufficient command of the Dutch language. The non-depressed older adults in the comparison group were included using similar criteria and were sourced from general practitioners. A face-to-face assessment was performed at baseline and after 2- and 6-years follow-up. All interviews and physical examinations were conducted by carefully selected research assistants, mainly consisting of psychologists and mental health care nurses. The research assistants received a 5 day training from an experienced and certified trainer before the baseline and follow-up assessments. All participants gave verbal and written informed consent before enrolment, and ethical approval was granted by Ethical Review Board of the VU-Medical Center, the Leiden University Medical Center, University Medical Center Groningen, and the Radboud University Medical Center in Nijmegen. The procedures followed were in accordance with the ethical standards of the responsible committees and with the Helsinki Declaration of 1975, as revised in 1983. A more detailed description of NESDO is given elsewhere.[15]

For the current study, we used data on PA at baseline and data on cognitive functioning which were gathered at baseline and at 2- and 6-year follow-up. Patients with complete data on PA and cognitive functioning at baseline were included, yielding 394 (77.3%) participants for the current analyses of whom 297 were depressed and 97 non-depressed. Of the depressed, a large majority had major depression (n = 282), of which 27% (n = 77) combined with dysthymia.

Measurements

Physical Activity (PA). Self-reported PA was assessed using the International Physical Activities Questionnaire (IPAQ).[16] The IPAQ measures PA as part of daily work and leisure time activities and is a validated questionnaire for assessing PA in older adults.[17] PA was defined as the ratio of energy expenditure during activity compared to rest, multiplied by the number of minutes performing the activity per week in metabolic equivalent minutes (MET-minutes).[18,19] To improve the interpretation of the strength of the associations with PA, the total MET minutes per week was included as standardized *z*-scores in the statistical models.

Cognitive functioning. Cognitive functioning was assessed using the following neuropsychological tests: the Mini Mental Status Examination (MMSE) for global cognitive functioning,[20] the short form of the Stroop color-word test,[21] the subtest digit span from the Wechsler Adult Intelligence Scale[22] and a 10-word version of the auditory verbal learning test.[23] In total, we determined 5 cognitive outcomes. Based on earlier exploratory analyses of these tests in the NESDO-data,[24] 4 cognitive domain scores were subsequently created: global cognitive functioning, verbal memory, interference-control and working memory.[25] Verbal memory, a test for memory function, comprised the total number of correct words on the 5 tasks and delayed recall task of the 10-word auditory verbal learning test. Interference-control, which is a component of executive functioning, comprised the interference score from the Stroop test, which was computed with the formula: $(t_{III} - 0.5 * (t_I + t_{II})) / (0.5 * (t_I + t_{II})) * 100\%$.[26] For our longitudinal analyses this variable was transformed by taking the natural logarithm (after adding a constant (50)) to make it approach a normal distribution and multiplied by -1, in order

for higher scores to represent better cognitive scores. Working memory comprised the total number of correct items of the forward and backward scores of the WAIS digit span, a measure of attention. For all 4 cognitive outcomes higher scores represent better performance. Finally, as the MMSE might be insufficient to detect mild cognitive decline,[27] we also created a compound cognitive score. We computed a compound Z-score by averaging the mean Z-scores all the 4 cognitive outcomes. Thus, z-scores were used in the longitudinal analyses to enable comparison of effect sizes among these 5 cognitive outcomes.

Depression. Depression was defined as major depression, dysthymia or minor depression in the past 6 months according to DSM-IV criteria.[28] Depression was assessed with a structured clinical interview that is designed for use in research settings with high validity for depressive disorders (Composite International Diagnostic Interview; CIDI; WHO version 2.1; lifetime version.[29,30]

Covariates. Covariates were selected based on the existing literature and clinical rationale. Variables were examined as potential confounders, including socio-demographics, physical health and lifestyle characteristics and neuropsychiatric characteristics. Socio-demographics included age, gender, partner status, and level of education. Level of education was specified as years of education. Physical health and lifestyle characteristics included alcohol consumption, cardiovascular disease risk, the number of chronic diseases, limitations in mobility, the presence of disabling pain, and the use of psychotropic medications. Alcohol use was categorized into drinking 0, $\leq$14, or >14 drinks per week based on the Alcohol Use Disorders Identification Test.[31] Cardiovascular risk score was assessed as previously defined in the Dubbo-study.[32] The number of chronic diseases (cardiac disease (e.g. myocardial infarction), peripheral atherosclerosis, hypertension, stroke, diabetes mellitus, COPD (asthma, chronic bronchitis or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis), cancer or any other disease) was assessed by means of a self-report questionnaire.[33] Self-reported limitations in mobility were assessed with the WHO-Disability Assessment Schedule (WHO-DASII) mobility subset which comprises 5 questions on mobility. Higher scores indicate higher disability. It has been validated and proven reliable in older, and depressed adults.[34] Pain was assessed using Chronic Graded Pain Scale-Dutch (CGPS, range 0-100), a self-report questionnaire that scores both pain intensity and disability due to pain.[35] Higher scores indicating more intense or disabling pain. It was categorized into 5 grades ranging from pain free (grade 0) to high intensity with severe disability (grade 4). To account for medication effects, we included use of psychotropics (Yes/No). Use of psychotropic medications was assessed at baseline by registration of the medication participants brought in and was coded using the Anatomic Therapeutic Chemical classification system.To control for neuropsychiatric symptoms, we included apathy symptoms and depression severity. Apathy was assessed using the 14-item Apathy Scale.[36] Severity of depressive symptoms was measured with the self-report Inventory of Depressive Symptoms (IDS).[37]

Statistical Analyses

For Table 1 and the illustration only (Figure 2A and B), we categorized PA at baseline by creating tertiles (low, moderate, and vigorous), whereas all other analyses were done on the continuous variable. The association of baseline characteristics with low, moderate, and vigorous PA was evaluated through 1-way ANOVA for normally distributed, continuous variables. A non-parametric test was used for continuous variables with non-normal distributions. The χ^2 test was used for categorical variables. A confidence interval of 95% was computed and *P*-values < .05 were considered statistically significant. For visual representation only (Figure 1), we longitudinally explored the impact of baseline PA tertiles (i.e. low, moderate and vigorous) on the compound-scores over time only.

The main aim of our study was to assess the potential differential effects of baseline PA on the rate of cognitive decline over 6-year follow-up stratified for depression. This was examined for 5 cognitive outcomes: MMSE-scores, interference-control, verbal memory, working memory, and their compound-score. For this purpose, in the total sample we firstly investigated the significance of the 3-way interaction term "PA* (continuous)*time* depression" for all cognitive outcomes in a basic model using linear mixed models (LMM). The basic model contained the following: PA (continuous) + time+ depression + PA * time * depression +age +gender + education. Next, in order to examine differential effects of baseline PA on the rate of cognitive decline, we investigated the significance of the interaction-term "PA (continuous)*time" stratified for depression in a stepwise fashion. Firstly we examined significance of the interaction in a basic model in both groups. The basic model contained the following: PA (continuous) + time + PA * time +age +gender + education (model 1). Only covariates that gave a change of $\geq$10% in the regression coefficient in Model 1 of the compound-score, were incorporated in the fully adjusted model for all cognitive outcomes (Model 2). Confounders were assessed separately for the depressed and non-depressed group. To test for potential multicollinearity in Model 2, we examined the variance inflation factor (VIF) scores. All variables had a VIF below 4 and therefore all variables were examined as confounders. We also globally examined the impact of different patterns of depression (never vs intermittent vs chronic depressed) on potential differential effects of baseline PA on the rate of decline of the compound score. Next, we performed attrition analyses comparing baseline characteristics of participants who did (n = 161) and did not (n = 233) drop out. In our supplementary analyses we determined the effects of time on all cognitive outcomes stratified for depression. The

Table 1. Baseline Characteristics in 394 Participants With Complete data According to Their PA and Cognitive Functioning at Baseline.

	Low PA N = 131	Moderate PA N = 131	Vigorous PA N = 132	P-value*
PA, MET minutes, median (IQR)	330 (0-693)	1782 (1440-2394)	5155 (3859-6760)	
Sociodemographic characteristics				
Age, mean (SD)	72.3 (7.8)	69.3 (6.9)	68.8 (6.1)	<0.001
Men, n (%)	40 (31)	40 (54)	36 (27)	<0.001
Married or with partner, n (%)	72 (55)	84 (64)	77 (58)	0.31
Education, years, mean (SD)	9.8 (3.3)	12.0 (3.8)	11.4 (3.5)	<0.001
Clinical characteristics				
Alcohol (none) n (%)	54 (42)	39 (30)	30 (23)	0.004
Cardiovascular disease risk median (IQR)	7.2 (3.4)	5.0 (3.1)	6.1 (3.3)	<0.001
Number of chronic diseases, mean (SD)	2.7 (1.8)	2.2 (1.6)	2.1 (1.4)	0.012
WHO-DAS mobility subset, median (IQR)	35 (35)	10 (25)	5 (20)	<0.001
Disabling pain†, (high disability), n (%)	27 (21)	18 (14)	16 (12)	0.013
Use of psychotropics (Yes), n (%)	115 (85)	98 (75)	86 (64)	<0.001
Neuropsychiatric characteristics				
IDS‡, points, median (IQR)	31 (18-41)	23 (10-36)	17 (7-28)	<0.001
Apathy scale, points, median (IQR)	18 (12-21)	15 (11-20)	12 (7-17)	<0.001
MMSE-score§, points, mean (SD)	27.8 (1.6)	28.3 (1.8)	28.1 (1.9)	0.007
Interference-control median, (IQR)	1.2 (0.9-1.8)	1.2 (0.8-1.4)	1.1 (0.9-1.5)	0.5
Verbal memory, mean (SD)	5.4 (2.3)	6.1 (2.3)	6.5 (2.2)	<0.001
Working memory, mean (SD)	12.9 (3.2)	14.1 (3.0)	13.7 (3.1)	0.001
Compound z-score, mean (SD)	−0.32 (1.0)	0.14 (1.0)	0.18 (0.91)	<0.001

Data are presented as n (%), mean (SD) or median (interquartile range (IQR)), when appropriate. Participants were included according to completeness of data for all variables.

* p-values based on chi-square test for categorical variables, ANOVA for normally distributed continuous variables and non-parametric test for non-normally distributed variables.

† Chronic Graded Pain Scale pain free–high disability, severely limiting (grade 0-4).

‡ Inventory of Depressive Symptomatology-Self Report version.

§ Mini Mental State Examination.

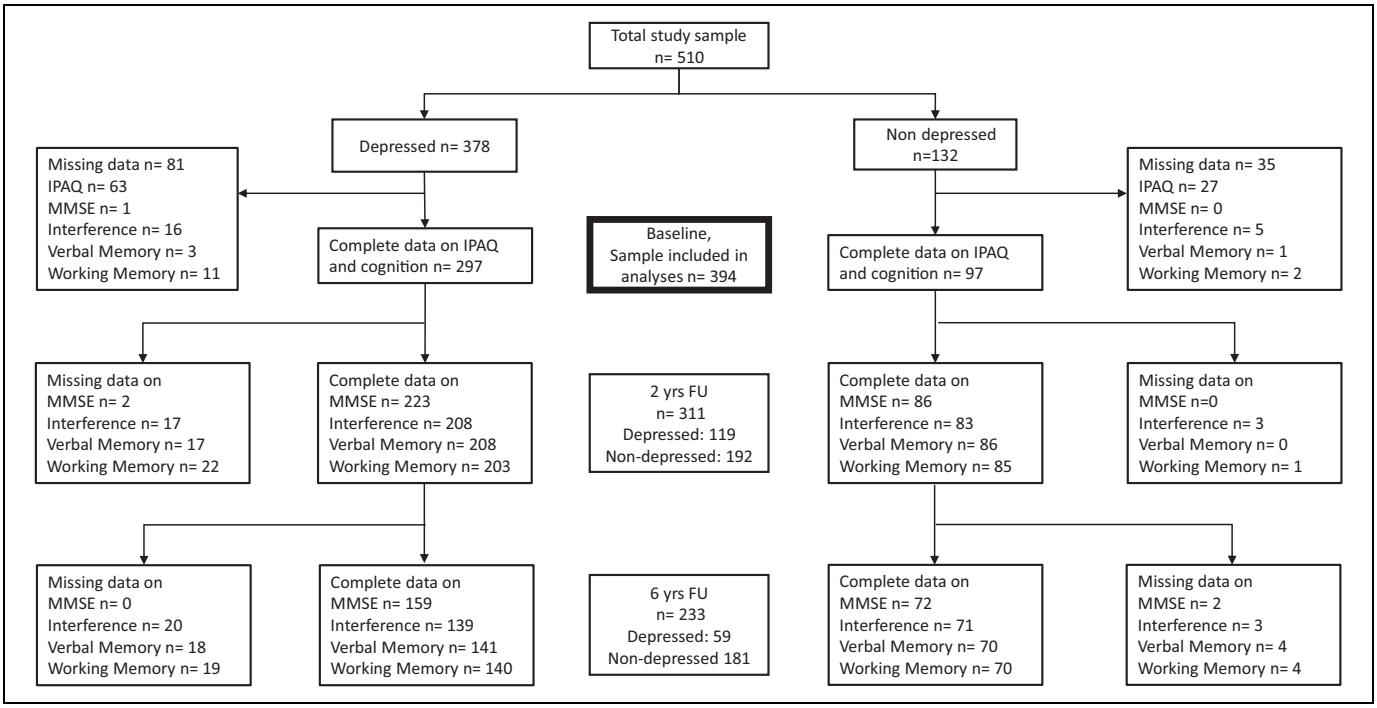

Figure 1. Flowchart of inclusion process.

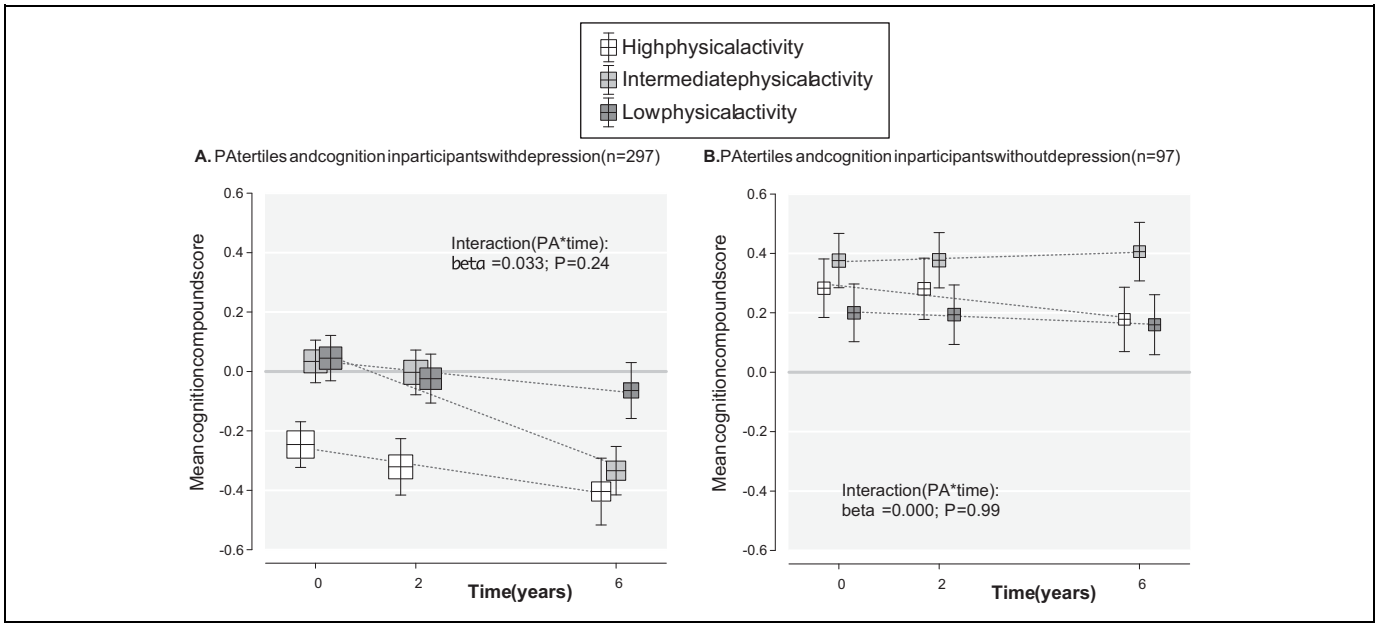

Figure 2. Association between baseline PA in tertiles (i.e., low, moderate, and vigorous) in relation to the compound-score with up to 6 years of follow up, in participants with depression [A] and without depression [B]. Error bars represent standard errors (SE), and the size of each box is proportional to the number of participants.

Table 2. A, Association Between Baseline PA and Cognitive Functioning Over 6 years of Follow-Up in 297 Depressed Participants of NESDO.

	MMSE score		Interference		Working memory		Verbal memory		Compound score	
	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
PA*time										
Model 1	0.063	0.07	0.024	0.59	-0.008	0.83	0.027	0.42	0.024	0.36
Model 2	0.072	0.07	0.127	0.02*	0.015	0.76	0.047	0.30	0.033	0.24

Betas and p-values were calculated by linear mixed models. * Significance level $p < 0.05$.
Model 1: adjusted for age, gender, and education.
Model 2: adjusted for age, gender, education, cardio vascular disease, disabling pain, IDS-score, and apathy score.

B, Association Between Baseline PA and Cognitive Functioning Over 6 Years of Follow-Up in 97 Non-Depressed Participants of NESDO.

	MMSE score		Interference		Working memory		Verbal memory		Compound-score	
	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
PA*time										
Model 1	-0.022	0.47	0.008	0.74	−0.009	0.76	0.031	0.23	-0.003	0.81
Model 2	-0.008	0.84	0.010	0.75	0.007	0.86	0.052	0.11	0.000	0.99

Betas and p-values were calculated by linear mixed models. * Significance level $p < 0.05$.
Model 1: adjusted for age, gender, and education.
Model 2: adjusted for age, gender, education, cardio vascular disease, WHO-DAS, and apathy score.

difference in the rate of decline between the depressed and non-depressed was tested using an interaction-term (depression*time) in the adjusted model. All analyses were performed using IBM SPSS Statistics version 23 (IBM Corp., USA). *P*-values < 0.05 were considered significant.

Results

Table 1 shows the sociodemographic, clinical and neuropsychiatric characteristics according to tertiles of level of PA at baseline. Overall, outcomes varied significantly across the tertiles for all variables except for partner status and interference-control. Post-

hoc analyses revealed that compared to the highest PA-tertile, participants in the lowest PA-tertile were significantly more often persons with higher age, a lower education level, higher alcohol consumption, and more disability. They also had more somatic and psychiatric comorbidity and lower levels of cognitive functioning except for interference-control (data not shown).

Association Between Baseline PA and Decline of Cognitive Functioning, Stratified for Depression

For all 5 cognitive outcomes, the Ps for interaction (PA*time* depression) were non-significant in the basic model (data not shown). Furthermore, neither in the depressed nor in the non-depressed, PA was associated with an overall differential decline in compound z-scores over time (Ps for interaction (PA*time): Model 1: *p*-value 0.36 and 0.81, and Model 2: 0.24 and 0.99 respectively) indicating that baseline PA was not associated with the speed of decline of any cognitive outcome over time in either group. Only for interference, in the depressed we found a significant p-value for interaction PA*time in the fully adjusted model ($p = 0.020$), but not for the non-depressed ($p = 0.75$). We therefore calculated the p-value for interaction (PA*time*depression) in the fully adjusted model with the confounders of Models 2 depressed and non-depressed combined. P-value was 0.01. For all other cognitive outcomes we found no significant associations: Ps for interaction (PA*time) were non-significant in both the depressed (Table 2A) and non-depressed (Table 2B).

Association Between PA and Compound-Score, Stratified for Depression-Patterns

Additionally, we globally examined the association between PA and decline of the compound-score, stratified for the course of depression: never depressed, depressed at 1 wave and depressed at two waves (baseline and 2 years of follow up). A total of 311 persons had data on depression at both waves. Results were similar as PA did not independently associate with decline of compound-scores in any group. Also Ps for interaction were non-significant in all groups (Appendix A).

In Figure 2, we present the results for the longitudinal association between baseline PA tertiles and compound score stratified for baseline depression using the multivariate adjusted model 2. Figure 2A and B show that there is no significant interaction between time and physical activity, neither in depressed patients (p PA*time = 0.24) nor in the non-depressed (p PA*time = 0.99). Just to enable visualization, we categorized subjects into 3 ordinal groups based on baseline physical activity, but the mixed analyses were based on the continuous data. Based on our hypothesis, we would have expected diverging lines with the steepest decline in the least psychically active elderly, but this was not what we found.

Attrition Analyses

Persons who were excluded from the analyses were significantly older ($p = 0.01$) and had worse performance on working memory ($p = 0.01$), but all other covariates did not differ significantly (data not shown). At 6-year follow-up, 161 participants of the baseline sample ($n = 394$) dropped out (41%). Persons who dropped out were among others more often depressed at baseline, older, without a partner, had lower education, more apathy symptomatology, higher severity of depressive symptoms, and lower cognitive functioning on all cognitive outcomes compared to the non-drop out group (Appendix B).

Supplementary Analyses

Time was associated with verbal and working memory, and compound-score, but not with MMSE-score and interference-control (data not shown). The extent of decline of any of the cognitive measures did not differ among the non-depressed and depressed (all Ps for depression*time > 0.05), except for working memory (*P*-interaction = 0.01). Only the depressed revealed decline in working memory over time (beta = −0.165, $p < 0.001$), but the non-depressed did not (beta = −0.015, $p = 0.73$) in our fully adjusted models (Appendix C1 and C2).

Discussion

We hypothesized that in a sample of Dutch non-demented older persons, higher levels of physical activity (PA) at baseline would be associated with a slower cognitive decline during 6 years of follow-up, especially in non-depressed older persons compared to depressed older persons. However, were unable to confirm our hypothesis. Namely in the depressed group, we only found a significant interaction of PA with time for interference control (multivariable model only), but not for 4 other cognitive outcomes. Furthermore, in the non-depressed, we found no significant associations for any cognitive outcome. Thus overall, the impact physical activity (PA) on long-term cognitive functioning was shown to be limited in our study, irrespective of the presence of depression. Depression at baseline appeared to worsen age-related decline of working memory only.

The inability to identify an active lifestyle as a protector for (steeper) cognitive decline on the long term appears to be in contrast with the results of 2 earlier major meta-analyses that demonstrated a clear association between PA and cognitive functioning.[6,7] However, it is well known that decreased PA may be a prodromal feature of dementia.[38,39] Despite the fact that the aforementioned meta-analyses only included prospective cohort studies (and therewith reducing the risk of reverse causation bias), a potential impact of reverse causation bias cannot be ruled out, partly due to a short follow-up duration.[7] This may have resulted in an overestimation of the putative protective effect of PA on decline of cognitive functioning in these meta-analyses. Interestingly, in a more recent meta-analysis of 19 prospective observational cohort studies investigating physical inactivity as a risk factor for dementia ($n = 404{,}840$, mean age 45.5 years, mean follow-up 14.9

years) the authors accounted for reverse causation bias.[40] No association between PA and dementia was seen, corroborating with our finding that the impact of PA at older age on cognitive functioning may be limited. Hypothetically, to prevent cognitive decline, an active lifestyle may need to be encouraged from an earlier age on. It was previously suggested that for this goal, insight in levels of PA over the lifespan may be more important than levels of PA at higher age assessed at a certain moment.[41] Also in one retrospective study, it was demonstrated that low levels of PA during teenage years may contribute the most to predicting cognitive impairment later in life compared to PA at higher age.[42] Likewise, as mentioned in the introduction, it has been suggested that PA plays an important role in reducing the risk of various diseases that have been associated with compromised cognitive and brain health (for example heart disease, stroke, and obesity). The development of these diseases and their effects on cognition and brain health may unfold over the course of several years to several decades.[41] However, interestingly, a recent population based study including persons aged 40 to 79 years revealed that also in older adults, the risk of low PA on, among others, cardiovascular disease mortality can be counteracted by increasing PA.[43] Whether this also applies to brain health remains to be determined.

A second explanation for our mainly negative results may be selective attrition, which may have underestimated our results. At baseline 116 persons did not have complete data on PA and all domains of cognitive functioning. Attrition at baseline appeared to be limited, however, during follow-up 161 persons (41%) dropped out, of which 138 depressed. Participants who probably developed cognitive decline or dementia likely had a higher chance to drop out as mean MMSE-scores of our study sample remained stable over time (mean MMSE-score at baseline 28.0 $\pm$ 1.9 and at 6 years follow up 28.1 $\pm$ 1.8). Also, persons suffering from depression had higher dropout-rates 138/297) compared to the non-depressed (74/97). This may have led to an underestimation of the effect, leading to type II statistical errors and the inability to demonstrate counteracting effect of depression on the long-term association between PA and cognitive decline. Besides selective attrition, also remission of depression may be responsible for stable MMSE-scores over time. Namely, of the 297 persons that suffered from depression at baseline, only 51 persons also suffered from depression at 6-year follow up. Because of these issues, we therefore attempted to gain further insight on the impact of different depression-patterns on the association between PA and long-term cognitive functioning using depression-data with 2 years of follow-up. Persons with low(er) PA-levels and depressive disorder at both time points did not have worse cognitive functioning at 6 years of follow-up compared to persons without depression or depression at one time point. Thus we also found no evidence that persons with persistent depression and lower PA-levels have worse cognitive performance on the long term. However, also these results must be considered with caution due to the aforementioned attrition.

Next, with regard to cognitive decline over time, we only demonstrated an association between time and decline of verbal memory, working memory and compound-score. The decline of cognitive functioning over time did not differ between the depressed and non-depressed group, except for working memory. Thus, the impact of baseline depression on the degree of cognitive decline over time may be limited. Again, besides selective attrition, remission of the depression may have impacted these results. As in our study, only mean baseline scores for interference-control ($p < 0.001$), and MMSE ($p = 0.04$) were significantly worse in the depressed compared to the non-depressed, it is unlikely that the absence of (steeper) decline in the depressed is explained by a floor effect. Previously, in older persons, depression has been linked with various aspects of cognitive functioning, but mainly with deficits in (verbal)[44] memory and executive functioning.[45] Information processing may be the core deficit in cognitive impairment in this population and may play a crucial role in these specific domains.[45]

Our study has several strengths and limitations. The major strengths of our study are the longitudinal, clinically orientated design and the use of various validated instruments. We adjusted for many relevant confounders with a far wider scope than only cardio-vascular associated factors as included in many previous studies.[6,46] The interaction effects with time enabled us to compare the extent of change of cognitive functioning according to baseline PA. Our main limitation has already been addressed in detail: our study suffered from high selective attrition. Next, we used baseline PA only as a time-invariant predictor in our analyses, as the study sample was too small and attrition too high to perform reliable time lag analyses (TLA) which may be more suited to explore potential causal dynamics compared to LMM. Furthermore, as participants broken down by baseline PA showed marked differences in many covariates (Table 1), there remains a risk of residual confounding. Also, we consider under representation of the non-depressed group compared to the depressed group as an important limitation. Unbalanced sizes of the study groups may have resulted in overestimation of the contrast between the 2 study groups. Next, the relatively small sample size and considerable attrition over time, limits the statistical power and generalizability to the general older population. Future studies with larger samples that are able to model the interplay between time-varying factors are needed to disentangle potential different associations between PA and long-term cognitive functioning in depressed and non-depressed older persons.

Finally, we used the IPAQ to determine the level of PA. Although in older adults the IPAQ is a validated questionnaire for assessing physical activity, it was previously noted that older adults may not adequately assess their range of activities, particularly low-intensity physical activity.[47] Smart devices for measuring real time physical activity in daily life may be more accurate and such measurement should be included in future studies.

Appendix A. Association Between PA and Compound Score Stratified for Depression Pattern.

	Never depressed		Depressed at T1 or T2		Depressed at T1 and T2	
	N = 83		N = 112		N = 116	
	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
PA*time						
Model 1	−0.004	0.81	−0.025	0.36	0.084	0.052
Model 2	−0.002	0.94	0.020	0.54	0.067	0.12

Only calculated in participants with data on T1 (baseline) and T2 (2 years of FU) (n = 311).
Betas were calculated by linear mixed models.
* Significance level $P < 0.05$.
Model 1: adjusted for age, gender, and education.
Model 2: adjusted for age, gender, education, cardio vascular disease, WHO-DAS, disabling pain IDS-score, and apathy score.

Appendix B. Baseline Characteristics of Participants (n = 394) Stratified for Drop-Out During 6 Years at Follow Up.

	No drop out	Drop out	P-value[a]
	N = 233	N = 161	
PA, MET minutes per week, median (IQR)	2133 (1167-4149)	1386 (377-3519)	0.04
Sociodemographic characteristics			
Age, mean (SD)	68.5 (6.2)	72.5 (7.6)	<0.001
Men, n (%)	85 (37)	61 (38)	0.78
Married or with partner, n (%)	150 (64)	83 (52)	
Education, years, mean (SD)	11.7 (3.6)	10.1 (3.5)	<0.001
Clinical characteristics			
Alcohol (none) n (%)	62 (26)	61 (38)	0.04
Cardiovascular disease risk median (IQR)	5.7 (3.3)	6.6 (3.5)	0.01
Number of chronic diseases, mean (SD)	2.2 (1.6)	2.4 (1.7)	0.22
WHO-DAS mobility subset, median (IQR)	7.5 (20)	20 (30)	<0.001
Disabling pain (high disability), n (%)	32 (14)	29 (18)	0.38
Use of psychotropics (Yes), n (%)	132 (70)	163 (85)	0.001
Neuropsychiatric characteristics			
Depression (Yes), n (%)	159 (68)	138 (86)	<0.001
IDS, points, median (IQR)	21 (8-33)	27 (15-39)	0.03
Apathy scale, points, median (IQR)	14 (9-19)	18 (13-21)	0.001
MMSE score, points, mean (SD)	28.3 (1.5)	27.4 (2.2)	<0.001
Interference control median, (IQR)	1.0 (0.8-1.4)	1.3 (1.0-1.8)	<0.001
Verbal memory, mean (SD)	6.5 (5.3)	5.3 (2.3)	<0.001
Working memory, mean (SD)	14.3 (3.2)	12.8 (2.8)	<0.001
Compound z-score, mean (SD)	−0.24 (0.94)	−0.35 (0.99)	<0.001

Data are presented as n (%), mean (SD) or median (interquartile range (IQR)), when appropriate. Participants were included according to completeness of data for all variables.
* p-values based on chi-square test for categorical variables, ANOVA for normally distributed continuous variables and non-parametric test for non-normally distributed variables.
† Chronic Graded Pain Scale pain free–high disability, severely limiting (grade 0-4).
Supplementary analyses:

Appendix C1. Association Between Time and Cognitive Functioning Over 6 Years of Follow-Up in 297 Depressed Participants of NESDO.

	MMSE score		Interference		Working memory		Verbal memory		Compound score	
Time	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Model 1	−0.039	0.21	−0.008	0.83	−0.126*	<0.001*	−0.142	<0.001*	−0.105	<0.001*
Model 2	−0.031	0.35	−0.010	0.82	−0.165*	<0.001*	−0.132	<0.001*	−0.102	<0.001*

Betas and *P*-values were calculated by linear mixed models.
* Significance level $P < 0.05$.
Model 1: adjusted for age, gender, and education.
Model 2: adjusted for age, gender, education, cardio vascular disease, disabling pain, IDS-score, and apathy score.

Appendix C2. Association Between Time and Cognitive Functioning Over 6 Years of Follow-Up in 97 Non-Depressed Participants of NESDO.

	MMSE score		Interference		Working memory		Verbal memory		Compound score	
Time	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Model 1	−0.005	0.90	−0.030	0.89	−0.020	0.61	−0.111	0.001*	−0.021	0.27
Model 2	−0.012	0.78	−0.021	0.55	−0.015	0.73	−0.111	0.002*	−0.015	0.48

Betas and p-values were calculated by linear mixed models.
* Significance level $P < 0.05$.
Model 1: adjusted for age, gender, and education.
Model 2: adjusted for age, gender, education, cardio vascular disease, WHO-DAS, and apathy score.

Conclusions and Clinical Implications

Despite the absence of a robust significant association between PA and cognitive decline, we do not consider our results to be an incentive to discourage PA at older age as it has been demonstrated that PA has a positive effect on a multitude of other health outcomes in this population (for instance longevity, lower risks of (hip)fractures and disability.[3,43] Hypothetically, to postpone decline of cognitive functioning, PA should be encouraged at younger age.[41] Finally, the decline of working memory over time was only present in the depressed, but not in non-depressed. By treating depression, this may be postponed, which should be determined in future research.

Declaration of Conflicting Interests

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