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Lack of physical activity, neuropsychiatric symptoms and the risk of incident mild cognitive impairment in older community-dwelling individuals

A prospective cohort study

Introduction

According to the 2015 World Alzheimer Report, over 46 million people worldwide have dementia, with an anticipated increase to 152 million individuals by 2050 (Patterson, 2018). Mild cognitive impairment (MCI) is considered the intermediate stage between normal cognitive aging and dementia. MCI constitutes a high risk state for progression to dementia, and its prevalence is estimated to range between 12% and 18% in persons aged ≥60 years (Petersen, 2016). Research has increasingly focused on modifiable lifestyle factors such as physical activity that may be effective in preventing or delaying the onset of cognitive impairment in the context of brain aging (Lautenschlager, Cox, & Ellis, 2019), and especially early disease stages such as subjective cognitive impairment or MCI are regarded as a "window of opportunity" for a potentially protective effect of physical activity on cognitive decline.

In line with this, the authors and others have reported that engaging in physical activity is associated with a decreased risk of developing new onset of MCI (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Yoneda et al., 2020; Krell-Roesch et al., 2016) and dementia (Podewils et al., 2005; Tan et al., 2017; Krell-Roesch et al., 2018), with a recent meta-analysis indicating a dose–response relationship between a higher degree of physical activity and lower risk of incident dementia (Xu et al., 2017). In turn, lack of engagement in physical activity and sedentary behavior is associated with higher odds of having MCI (Vancampfort et al., 2018), and is also regarded as a risk factor for cognitive decline in old age (Falck, Davis, & Liu-Ambrose, 2017); albeit, conflicting (Maasakkers et al., 2020) or only sex-specific findings (Whitaker et al., 2021) have been reported. Nevertheless, a recently published report by the Lancet commission lists physical inactivity as one of 12 modifiable risk factors for dementia (Livingston et al., 2020). In addition, neuropsychiatric symptoms such as depression, apathy, or anxiety are very common in older adults with or without cognitive impairment (Geda et al., 2008; Lyketsos et al., 2002). Furthermore, these are also well-established risk factors of incident MCI or dementia (Forrester, Gallo, Smith, & Leoutsakos, 2016; Geda et al., 2014; Pink et al., 2015; Teng, Lu, & Cummings, 2007).

Little is known about the longitudinal association and interaction between physical activity and neuropsychiatric symptoms in predicting the risk of incident MCI in older community-dwelling adults. The aim of this study was thus to examine the association between lack of engaging in late-life physical activity and presence of neuropsychiatric symptoms, both separately and combined, with the outcome of incident MCI. The authors hypothesized that participants who do not report engaging in physical activity and have neuropsychiatric symptoms would be at higher risk of developing incident MCI than participants who report engaging in physical activity and do not have neuropsychiatric symptoms.

Methods

Study sample and design

This prospective cohort study was conducted in the setting of the ongoing, pop-

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ulation-based Mayo Clinic Study of Aging (MCSA) in Olmsted County, Minnesota, USA (Roberts et al., 2008). At baseline, 3083 cognitively unimpaired individuals aged ≥ 50 years with available information on physical activity within the preceding 1 year, presence or absence of neuropsychiatric symptoms, and data available on covariates were included. Participants were then followed forward in time for a median of 6.3 years to the outcome of incident MCI. The MCSA protocols have been approved by the institutional review boards (IRB) of the Mayo Clinic and Olmsted Medical Center in Rochester, MN, USA. All participants provided written informed consent.

Neurocognitive evaluation and diagnosis of incident MCI (outcome variable)

Participants underwent a face-to-face evaluation including a neurological examination, a study coordinator visit, and neuropsychological testing (Roberts et al., 2008). Briefly, the neurological evaluation comprised a neurological history review, administration of the Short Test of Mental Status (Kokmen, Smith, Petersen, Tangalos, & Ivnik, 1991), and a neurological examination. The study coordinator visit included the Clinical Dementia Rating Scale® (CDR) (Morris, 1993). Neuropsychological testing was administered by a psychometrist in order to assess performance in four cognitive domains: memory (delayed recall trials from Auditory Verbal Learning Test [Rey, 1964], Wechsler Memory Scale-Revised [Wechsler, 1987], Logical Memory and Visual Reproduction subtests); language (Boston Naming Test [Kaplan, Goodglass, & Weintraub, 2001], category fluency [Lucas et al., 1998]); visuospatial skills (Wechsler Adult Intelligence Scale-Revised [Wechsler, 1981], Picture Completion and Block Design subtests); and attention/executive function (Trail-Making Test Part B [Reitan, 1958], Wechsler Adult Intelligence Scale-Revised [Wechsler, 1981], Digit Symbol Substitution subtest). An expert consensus panel consisting of physicians, study coordinators, and neuropsychologists reviewed the results for each participant and determined whether a participant was cognitively unimpaired (CU) or had cognitive impairment. Individuals were classified as CU based on normative data developed on a different sample in this community (Ivnik et al., 1992a, b, c; Malec et al., 1992). For MCI, the revised Mayo Clinic criteria for MCI (Petersen, 2004; Winblad et al., 2004) were used: (1) cognitive concern expressed by a physician, informant, participant, or study coordinator; (2) impairment in one or more cognitive domains (memory, attention/executive function, language, or visuospatial skills); (3) essentially normal functional activities; and (4) absence of dementia. Participants with MCI had a CDR score of 0 or 0.5; however, the final diagnosis of MCI was based on all available data.

Measurement of physical activity (predictor variable)

Physical activity within the previous year was measured at baseline using a self-reported questionnaire (Geda et al., 2010). The questionnaire was derived from two validated instruments, the 1985 National Health Interview Survey and the Minnesota Heart Survey intensity codes (Folsom et al., 1985; National Center for Health Statistics (U.S.), Moss, & Parsons, 1986). The questionnaire distinguished between three intensity levels and provided examples of physical activities for each level: (1) light physical activity such as leisurely walking or slow dancing; (2) moderate physical activity such as hiking or swimming; and (3) vigorous physical activity such as jogging or playing tennis singles. Participants were asked to provide information about the frequency with which they carried out these activities: ≤ 1 time per month, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, and daily. If a participant engaged in more strenuous activity more often than light activity, then their light activity was adjusted to be the same amount of times as the more strenuous activity. The same adjustment was made for moderate activity. This was done to avoid misleading results as someone may report not engaging in light activity, for example, and at the same time, be doing a lot of moderate or vigorous activity. If we did not make this adjustment, this person would appear sedentary in the light activity analyses, when this is not the case. Furthermore, if a participant reported engaging in physical activity at a given intensity level 2–3 times/month or less within 1 year of baseline assessment, then this was considered as not engaging in/lack of physical activity. Previous research has shown that the physical activity questionnaire used in the MCSA has moderate to good internal consistency, and test–retest correlation coefficients range between 0.33 for vigorous intensity activity and 0.50 for moderate intensity activity (Geda et al., 2010).

Measurement of neuropsychiatric symptoms (predictor variable)

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q; [Kaufer et al., 2000]). The NPI-Q was administered as a structured interview to an informant by a study coordinator and assessed the presence/absence of 12 emotional behaviors (i.e., depression, anxiety, apathy, agitation, delusions, hallucinations, euphoria, disinhibition, irritability, aberrant motor behavior, sleep/nighttime disturbance behavior, and eating/appetite). In addition, self-reported neuropsychiatric symptoms were assessed using the Beck Depression Inventory (BDI–II; [Beck, Steer, & Brown, 1996]) and Beck Anxiety Inventory (BAI; [Beck & Steer, 1990]). The BDI–II measures common symptoms of depression, such as feelings of guilt or loss of interest, over the preceding 2 weeks. The BAI measures common anxiety symptoms, such as nervousness or fear of losing control, over the preceding week. Both inventories are validated and have 21 items. The severity of each item is rated on a Likert-type scale ranging from 0 to 3, with the total score thus ranging from 0 to 63. A higher score indicates higher severity of depressive and anxiety symptoms, respectively.

Assessment of confounding variables

In addition to traditional confounders (i.e., age, sex, and education), the study also adjusted the analyses for global cog-

nitive function, medical comorbidity as assessed through the weighted Charlson Index (Charlson, Pompei, Ales, & MacKenzie, 1987), and apolipoprotein E (APOE) ε4 genotype status, which was determined using standard methods.

Statistical analysis

The authors tested for additive interactions using jackknife resampling and calculated Cox proportional hazards models with age as the time scale to assess the association between two predictors of interest (i.e., self-reported lack of engaging in light, moderate, and vigorous intensity physical activity within 1 year of baseline assessment; presence of neuropsychiatric symptoms as measured by the NPI-Q; and clinical depression and clinical anxiety as indicated by BDI–II total score ≥ 13 and BAI total score ≥ 10) and the outcome of interest (i.e., incident MCI). When statistically significant interactions were detected, the risk of incident MCI between four groups of participants was compared: 1) absence of neuropsychiatric symptoms/engaging in physical activity (reference group); 2) presence of neuropsychiatric symptoms/engaging in physical activity; 3) absence of neuropsychiatric symptoms/not engaging in physical activity; and 4) presence of neuropsychiatric symptoms/not engaging in physical activity. All analyses were adjusted for sex, education, global cognition, medical comorbidities, and APOE ε4 carrier status. All statistical analyses were performed using the conventional two-tailed alpha level of 0.05 and performed with SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 3083 participants with a mean (standard deviation) age of 72.41 (9.72) years were included in this study; 50.9% of the sample were males and 27.8% were APOE ε4 carriers. After a median follow-up of 6.3 years, 599 participants developed incident MCI. In all, 14.2% of participants reported not engaging in light intensity physical activity, 42.0% reported not engaging in moderate intensity physical activity, and 85.6% reported not engaging in vigorous intensity physical activity within 1 year prior to baseline assessment. The most frequent neuropsychiatric symptoms present in the total sample were depression (9.2%), irritability (6.8%), sleep/nighttime disturbance behavior (5.8%), anxiety (4.8%), and apathy (3.8%). Clinical depression (BDI-II total score ≥ 13) was present in 5.4% and clinical anxiety (BAI total score ≥ 10) was present in 6.0% of participants (**Table 1**).

Individuals who did not engage in moderate intensity physical activity (HR [95% CI]; 1.18 [1.00, 1.39], $p = 0.047$) had a statistically significantly increased risk of incident MCI. Having anxiety (1.52 [1.05, 2.20], $p = 0.028$), apathy (1.92 [1.41, 2.60], $p < 0.001$), and depression (1.71 [1.35, 2.16], $p < 0.001$), as well as clinical depression (1.47 [1.09, 1.97], $p = 0.012$), were also associated with an increased risk of incident MCI (**Table 2**).

There were no significant additive interactions between light intensity physical activity and neuropsychiatric symptoms or between moderate intensity physical activity and neuropsychiatric symptoms in predicting the risk of incident MCI. There were statistically significant additive interactions between vigorous intensity physical activity and sleep/nighttime disturbance behavior, clinical depression, and clinical anxiety in predicting the risk of incident MCI, i.e., participants who did not engage in vigorous intensity physical activity in the presence of sleep/nighttime disturbance behavior (1.61 [1.07, 2.43], $p = 0.021$), clinical depression (1.98 [1.34, 2.92], $p < 0.001$), or clinical anxiety (1.63 [1.11, 2.41], $p = 0.013$) had an increased risk

Abstract

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Lack of physical activity, neuropsychiatric symptoms and the risk of incident mild cognitive impairment in older community-dwelling individuals. A prospective cohort study

Abstract

The present study examined the longitudinal association and interaction between lack of engaging in physical activity (PA) and presence of neuropsychiatric symptoms (NPS) with the risk of incident mild cognitive impairment (MCI). The authors conducted a prospective cohort study in the setting of the population-based Mayo Clinic Study of Aging in Minnesota, USA, involving 3083 cognitively unimpaired persons aged ≥ 50 years (1570 males; median age, 74 years). Predictors included: lack of engaging in light, moderate, and vigorous intensity PA within 1 year of baseline assessment as measured by a self-reported questionnaire; and presence of NPS (agitation, anxiety, apathy, appetite change, sleep/nighttime disturbance, depression, irritability, clinical depression, clinical anxiety) as measured by standardized tools. When the authors detected a statistically significant interaction, they compared the risk of incident MCI between four groups of participants (no NPS/engaging in PA = reference group; NPS/engaging in PA; no NPS/not engaging in PA; NPS/not engaging in PA) by calculating hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazard models adjusted for age (as time scale), sex, education, global cognition, medical comorbidities, and apolipoprotein E ε4 status. After a median follow-up of 6.3 years, 599 participants developed incident MCI. Not engaging in vigorous intensity PA and having sleep/nighttime disturbance (HR [95% CI], 1.61 [1.07, 2.43]; $p = 0.021$), clinical depression (1.98 [1.34, 2.92]; $p < 0.001$) or clinical anxiety (1.63 [1.11, 2.41]; $p = 0.013$) was associated with an increased risk of incident MCI as compared to the reference group. Thus, the combined presence of lack of vigorous intensity physical activity with sleep/nighttime disturbance behavior, clinical depression, or clinical anxiety was greater than the expected arithmetic sum of their independent effects. Neuropsychiatric symptoms appear to be a stronger driving force of incident MCI than lack of physical activity.

Keywords

Lifestyle · Depression · Anxiety · Longitudinal · Cognition

Table 1 Participant demographics at baseline

Variable	Remained CU (*N* = 2484)	Incident MCI (*N* = 599)	Total (*N* = 3083)
Age			
Mean (SD)	70.85 (9.83)	78.85 (6.84)	72.41 (9.72)
Median (IQR)	72.21 (63.74, 77.62)	79.75 (74.47, 83.76)	73.62 (65.37, 79.75)
Male sex, N (%)	1279 (51.5)	291 (48.6)	1570 (50.9)
Education, years			
Mean (SD)	14.83 (2.58)	13.79 (2.71)	14.63 (2.64)
Median (IQR)	15.00 (12.00, 16.00)	13.00 (12.00, 16.00)	14.00 (12.00, 16.00)
APOE ε4 carrier, N (%)	647 (26.0)	209 (34.9)	856 (27.8)
Charlson Index			
Mean (SD)	2.62 (2.78)	3.74 (3.10)	2.84 (2.88)
Median (IQR)	2.00 (1.00, 4.00)	3.00 (2.00, 5.00)	2.00 (1.00, 4.00)
Global cognition z-score			
Mean (SD)	0.22 (0.89)	–0.90 (0.93)	0.00 (1.00)
Median (IQR)	0.26 (–0.40, 0.86)	–0.89 (–1.45, –0.31)	0.05 (–0.66, 0.70)
Light intensity PA, N (%)			
Not engaging	328 (13.2)	111 (18.5)	439 (14.2)
Engaging	2156 (86.8)	488 (81.5)	2644 (85.8)
Moderate intensity PA, N (%)			
Not engaging	1002 (40.3)	292 (48.7)	1294 (42.0)
Engaging	1482 (59.7)	307 (51.3)	1789 (58.0)
Vigorous intensity PA, N (%)			
Not engaging	2098 (84.5)	542 (90.5)	2640 (85.6)
Engaging	386 (15.5)	57 (9.5)	443 (14.4)
Agitation, N (%)	52 (2.1)	14 (2.3)	66 (2.1)
Anxiety, N (%)	117 (4.7)	30 (5.0)	147 (4.8)
Apathy, N (%)	71 (2.9)	46 (7.7)	117 (3.8)
Appetite change, N (%)	80 (3.2)	27 (4.5){1}	107 (3.5){1}
Nighttime behavior, N (%)	105 (4.7){266}	54 (10.8){98}	159 (5.8){364}
Delusions, N (%)	2 (0.1)	3 (0.5)	5 (0.2)
Depression, N (%)	204 (8.2){1}	81 (13.5)	285 (9.2){1}
Disinhibition, N (%)	15 (0.6)	10 (1.7)	25 (0.8)
Euphoria, N (%)	11 (0.4)	3 (0.5)	14 (0.5)
Hallucinations, N (%)	0 (0.0)	1 (0.2)	1 (0.0)
Irritability, N (%)	162 (6.5)	48 (8.0)	210 (6.8)
Motor behavior, N (%)	14 (0.6)	3 (0.5)	17 (0.6)
BDI-II score ≥ 13	117 (4.7){12}	49 (8.2){2}	166 (5.4){14}
BAI score ≥ 10	131 (5.3){5}	52 (8.7){3}	183 (6.0){8}

CU cognitively unimpaired, *MCI* mild cognitive impairment, *SD* standard deviation, *IQR* interquartile range, *PA* physical activity, ***not engaging*** participant reported engaging in physical activity 2–3 times/month or less within 1 year of baseline assessment, *BDI-II* Beck Depression Inventory II, *BAI* Beck Anxiety Inventory, *N* number of persons with missing information

Table 2 Associations between lack of physical activity and incident mild cognitive impairment (MCI), as well as between neuropsychiatric symptoms and incident MCI

Risk factor	HR (95% CI)	*p*
Lack of physical activity		
No light PA	1.22 (0.98, 1.50)	0.070
No moderate PA	1.18 (1.00, 1.39)	**0.047**
No vigorous PA	1.27 (0.96, 1.67)	0.095
Neuropsychiatric symptoms		
Agitation	1.24 (0.73, 2.12)	0.428
Anxiety	1.52 (1.05, 2.20)	**0.028**
Apathy	1.92 (1.41, 2.60)	**< 0.001**
Appetite change	1.21 (0.82, 1.79)	0.335
Nighttime behavior	1.29 (0.96, 1.71)	0.088
Depression	1.71 (1.35, 2.16)	**< 0.001**
Irritability	1.20 (0.89, 1.62)	0.226
BDI-II score ≥ 13	1.47 (1.09, 1.97)	**0.012**
BAI score ≥ 10	1.26 (0.94, 1.68)	0.118

HR hazard ratio, *CI* confidence interval. *No PA* Participant reported engaging in physical activity 2–3 times/month or less within one year of baseline assessment. *BDI-II* Beck Depression Inventory II, *BAI* Beck Anxiety Inventory. *p* indicates statistical significance. Adjusted for age as the time scale, sex, education, global cognition, medical comorbidities, and apolipoprotein E ε4 genotype status. Delusions, disinhibition, euphoria, hallucinations, and motor behavior not displayed due to low counts

of incident MCI as compared to the reference group (**Table 3**).

Discussion

Here the authors report a synergistic additive interaction between lack of engaging in vigorous intensity physical activity and sleep/nighttime disturbance behavior, clinical depression, or clinical anxiety in increasing the risk of incident MCI in community-dwelling persons aged 50 years and older. Thus, the combined presence of lack of vigorous intensity physical activity with sleep/nighttime disturbance behavior, clinical depression, or clinical anxiety was greater than the expected arithmetic sum of their independent effects. However, statistically significant additive interactions between light or moderate intensity physical activity and neuropsychiatric symptoms in predicting the risk of incident MCI were not observed. In general, neuropsychiatric symptoms appear to be a stronger driving force of incident MCI than lack of physical activity.

To date, little is known about the longitudinal association and potential interactions between physical activity and neuropsychiatric symptoms in predicting the risk of incident MCI. Few studies have been published that examined interactions between physical inactivity or sedentary behavior and other lifestyle factors with cognitive decline. For example, US investigators reported that low sedentary behavior and high cardiorespiratory fitness interacted in preserving cognitive function

Table 3 Associations between the combination of neuropsychiatric symptoms and vigorous intensity physical activity and the outcome of incident mild cognitive impairment

Groups	No. at risk	No. of events	HR (95% CI)	*p*	Interaction *p*
Night. behavior–/PA+	388	46	Reference	N/A	*0.011*
Night. behavior+/PA+	22	4	0.46 (0.16, 1.28)	0.136	N/A
Night. behavior–/PA–	2172	401	1.07 (0.78, 1.46)	0.670	N/A
Night. behavior+/PA–	137	50	1.61 (1.07, 2.43)	*0.021*	N/A
BDI-II–/PA+	423	57	Reference	N/A	*< 0.001*
BDI-II+/PA+	19	0	N/A	N/A	N/A
BDI-II–/PA–	2480	491	1.09 (0.82, 1.44)	0.551	N/A
BDI-II+/PA–	147	49	1.98 (1.34, 2.92)	*< 0.001*	N/A
BAI–/PA+	429	56	Reference	N/A	*0.001*
BAI+/PA+	13	1	0.19 (0.03, 1.41)	0.105	N/A
BAI–/PA–	2463	488	1.15 (0.87, 1.52)	0.338	N/A
BAI+/PA–	170	51	1.63 (1.11, 2.41)	*0.013*	N/A

NPS– absence of NPS; *NPS+* presence of NPS; *PA–* not engaging in physical activity, i.e., participant reported engaging in physical activity 2–3 times/month or less within 1 year of baseline assessment; *PA+* engaging in physical activity; *BDI-II* Beck Depression Inventory II; *BAI* Beck Anxiety Inventory; *HR* hazard ratio; *CI* confidence interval. Reference group, *HR* 1.00. *N/A* not applicable or available. Adjusted for age as the time scale, sex, education, global cognition, medical comorbidities, and apolipoprotein E ε4 genotype status. Only models with significant additive interaction are presented

in persons aged ≥60 years (Edwards & Loprinzi, 2017). Researchers from the Rush Memory and Aging Project observed that accelerometer-measured physical activity and self-reported cognitive activity had significant interactive effects on memory in older cognitively unimpaired adults (Halloway, Schoeny, Wilbur, & Barn, 2020). With regard to neuropsychiatric symptoms, a cross-sectional study from South Korea found that depression mediates the inverse relationship between physical activity and cognitive impairment among older adults (Jin et al., 2018); and another study from China reported that a higher amount of leisure-time physical activity was associated with less neuropsychiatric symptoms in community-dwelling adults with cognitive impairment (Chiu et al., 2014). Similarly, US researchers reported that an intensive continuous activity programming in dementia patients was associated with decreased agitation and improved sleep (Volicer, Simard, Pupa, Medrek, & Riordan, 2006). One intervention study revealed a reduction in aggressive behavior in dementia patients after they underwent a walking program (Holmberg, 1997), and a randomized clinical trial showed that an intervention combining physical activity with nighttime environment improvement had a beneficial impact on sleep and agitation in nursing home residents (Alessi, Yoon, Schnelle, Al-Samarrai, & Cruise, 1999). In line with this, a recent review concluded that engagement in physical activity had a positive impact on neuropsychiatric symptoms, particularly depression and sleep disturbance, in patients with Alzheimer's disease (Veronese, Solmi, Basso, Smith, & Soysal, 2019), and researchers from Japan reported that a combination of poor sleep quality and physical inactivity was associated with significantly decreased cognitive performance in a large sample of over 5000 community-dwelling older adults (Nakakubo et al., 2017). These studies are partly in line with the authors' observation that lack of engaging in vigorous intensity physical activity and sleep/nighttime disturbance behavior or clinical depression are associated with higher risk of developing MCI. Of note, the present study considered participants who reported engaging in physical activity at a given intensity level (i.e., light, moderate and vigorous) 2–3 times per month or less as having a lack of physical activity. This must be distinguished from sedentary behavior, which includes, for example, sitting activities such as watching TV or working on a computer. Lack of engaging in physical activity, as assessed in this research, and sedentary behavior are thus different constructs. More research is needed to also examine the association between sedentary behavior, neuropsychiatric symptoms, and the risk of incident MCI.

The authors did not examine potential mechanisms that may explain the observed interaction between lack of vigorous intensity physical activity and sleep/nighttime disturbance behavior, clinical depression, or clinical anxiety in increasing the risk of incident MCI. Previous research has shown that engaging in physical activity may be associated with brain health through various mechanisms (Cabral et al., 2019), including but not limited to increased release of neurotrophic brain factors such as brain-derived neurotrophic factor (Knaepen, Goekint, Heyman, & Meeusen, 2010), enhanced synaptogenesis and neurogenesis (Vecchio et al., 2018), increased cerebral blood flow (Nishijima, Torres-Aleman, & Soya, 2016), decreased vascular risk factors (Barnes & Corkery, 2018), and a generally healthy lifestyle of physically active persons that may also show in abstaining from smoking and adhering to a healthy diet or other health-enhancing behaviors. In contrast, persons who do not engage in physical activity may not benefit from these effects. Furthermore, the presence of neuropsychiatric symptoms has been linked to cognitive impairment via different pathways, i.e.,: 1) an etiologic pathway indicating that neuropsychiatric symptoms lead to cognitive impairment by affecting the pathology of the brain; 2) a shared risk factor pathway indicating that neuropsychiatric symptoms are not directly associated with cognitive impairment but that there is another genetic or environmental factor (confounder) that causes both emergence of neuropsychiatric symptoms and cognitive impairment; 3) a reverse causality pathway indicating that neuropsychiatric symptoms may be a non-cognitive manifestation of, or psychological reaction to, cognitive impairment and its underlying effect on brain pathology; and 4) an interaction pathway indicating the existence of a synergistic interaction between neuropsychiatric symptoms and a biological

factor that leads to cognitive impairment (Geda et al., 2013). Of note, as this was an observational study, reverse causality is also a possible explanation of its findings. According to this, persons who are in the very early disease stages without symptoms of MCI may engage in physical activity, particularly of vigorous intensity, to a lesser extent and may be more likely to report neuropsychiatric symptoms than persons who are not in early disease stages. In addition, the authors' conclusion that neuropsychiatric symptoms appear to be a stronger driving force of incident MCI than lack of physical activity could also be due to a potentially more robust assessment of neuropsychiatric symptoms than physical activity in this study. Another potential explanation might be that a large number of distinct neuropsychiatric symptoms was investigated, whereas only three rather broad physical activity parameters were utilized.

The strengths of this study include its large, population-based sample and a rigorous analysis with adjustment for traditional confounders as well as cognition, medical comorbidities, and APOE ε4 genotype status which is a genetic risk factor for Alzheimer's disease. Limitations pertain to the observational study design. Thus, the authors are not able to make conclusions regarding cause and effect based on their findings. As mentioned above, their findings imply that a combination of lack of physical activity, particularly of vigorous intensity, and the presence of neuropsychiatric symptoms may lead to increased risk of MCI, or that persons who will eventually develop MCI are more likely to not engage in physical activity and report neuropsychiatric symptoms several years before MCI onset. Another main limitation pertains to the physical activity assessment, which was carried out using a self-reported questionnaire and may thus be prone to recall bias. The questionnaire items were derived from validated surveys that were used in other studies before and, as previously reported by the authors, their questionnaire has moderate to good internal consistency (Geda et al., 2010). However, the questionnaire only assesses frequency of engaging in physical activity at three different intensities. It does not record volume or duration of physical activity (e.g., minutes per session), even though the volume of physical activity engagement is commonly used in recommendations on physical activity such as the World Health Organization (WHO) or American College of Sports Medicine (ACSM) guidelines and would be necessary to estimate energy expenditure. In addition, the intensity examples provided in the questionnaire might be misleading to some participants, e.g., one can swim with high intensity and play tennis singles with moderate intensity. This could have introduced a certain amount of bias, and the concepts of the different physical activity intensities may not have been clear to all participants.

In conclusion, the authors observed an additive interaction between lack of engaging in vigorous intensity physical activity and sleep/nighttime disturbance behavior, clinical depression, or clinical anxiety in further increasing the risk of incident MCI among cognitively unimpaired, community-dwelling adults aged 50 years and older. More research, preferably with longitudinal design, is needed to confirm these findings and to also examine potential mechanisms that may underlie this relationship.

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Declarations

Conflict of interest. W.K. Kremers receives research funding from the Department of Defense, NIH, Astra Zeneca, Biogen, and Roche. M.M. Machulda receives research funding from the NIH. M.M. Mielke served as a consultant to Eli Lilly, received unrestricted research grants from Biogen, Lundbeck, and Roche, and receives research funding from the NIA, NIH, and the Department of Defense. D.S. Knopman serves on a Data Safety Monitoring Board for the Dominantly Inherited Alzheimer Network (DIAN) study and is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California. R.C. Petersen consults for Roche Inc, Merck Inc, Genentech Inc, Eisai, Inc, Biogen Inc, and GE Healthcare and receives royalties from Oxford University Press for the publication of Mild Cognitive Impairment. M. Vassilaki received research funding from Roche, and currently receives research funding from NIH and Biogen. She has equity ownership in Abbott Laboratories, Johnson and Johnson, Medtronic, and Amgen. Y.E. Geda receives funding from the NIH and Roche and served on the Lundbeck Advisory Board. J. Krell-Roesch, J.A. Syrjanen, J. Bezold, S. Trautwein, B. Barisch-Fritz, and A. Woll declare that they have no competing interests.

All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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