The Importance of Engaging in Physical Activity in Older Adulthood for Transitions between Cognitive Status Categories: A Coordinated Analysis of Fourteen Longitudinal Studies

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Abstract

Background. Given increasing incidence of cognitive impairment and dementia, further understanding of modifiable factors contributing to increased healthspan is crucial. Extensive literature provides evidence that physical activity (PA) delays the onset of cognitive impairment and dementia; however, it is unclear if engaging in PA in older adulthood is sufficient to impact progression through cognitively impaired states.

Methods. Applying a coordinated analysis approach, this project independently analyzed fourteen longitudinal studies of older adults (total N = 52,039; mean baseline age range across studies = 69.9-81.73) from North America and Europe using multi-state survival models to estimate the impact of engaging in PA on cognitive status transitions (non-impaired, mildly impaired, severely impaired) and death. Multinomial regression models were fit to estimate life expectancy (LE) based on American PA recommendations. Meta-analyses provided the pooled effect sizes for the role of PA on each transition and estimated LEs.

Results. Controlling for baseline age, sex, education and chronic conditions, analyses revealed that more PA is consistently associated with decreased risk of transitioning from non-impaired to mildly impaired cognitive functioning and death, as well as substantially longer life expectancy. Results also provided evidence for a protective effect of PA after onset of cognitive impairment, though between-sample heterogeneity suggests a less robust association.

Conclusions. These results yield reliable evidence for the importance of engaging in PA in later adulthood for physical and cognitive health, and compelling evidence for maintaining cognitive functioning and a rationale for motivating older adults to engage in PA.

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Introduction

Given shifting demographics worldwide, researchers and the public are concerned with factors that contribute to increased longevity and, in particular, increased healthspan. As Alzheimer's disease is one of the leading causes of morbidity and mortality in older adults (1), further understanding of modifiable factors that protect against cognitive changes characteristic of Alzheimer's disease and other dementias is imperative. For example, delaying the onset of dementia by as little as one year is projected to reduce the number of dementia cases in 2050 by over 9 million, and substantially decrease the global financial burden associated with dementia care (1–3).

A substantial body of observational and experimental research shows that physical activity (PA) moderates declines in cognitive functioning (*see reviews,* 4–6) by facilitating neural plasticity processes (*see expert consensus report,* 7), such as increasing hippocampal volume (8). A meta-analysis synthesizing prospective studies examining the association between PA and risk of cognitive decline in healthy older adults found that both vigorous (-38%) and low-to-moderate (-35%) PA were consistently associated with decreased risk of cognitive decline at follow-up occasions (10). Research also suggests that PA may be protective for individuals living with Mild Cognitive Impairment (MCI; 11) and dementia (12,13), which is consistent with autopsy research indicating that PA may assist in maintaining function despite accumulation of dementia pathology (i.e., cognitive reserve) (14).

However, delineating the relative importance of PA in the progression of cognitive changes due to non-pathological and pathological aging is challenging because the approaches, based on autopsy data and using growth curve and cox regression models, are not typically able to determine the timing of when PA is most critical, or if the impact of engaging in PA in older adulthood is of a magnitude to impact cognitive status transitions (e.g., non-impaired, mildly

impaired, and severely impaired cognitive functioning). Further understanding of protective factors during different stages of cognitive aging is critical, as individuals do not typically transition from a state of non-impaired cognitive functioning directly to Alzheimer's disease; the insidious nature of the disease commonly results in a transitional phase in which cognitive decline is more substantial than that observed in normal aging but not severe enough to impact activities of daily living. This intermediate phase is defined as Mild Cognitive Impairment (MCI; Petersen et al., 1999). Research suggests that cognitive decline and associated neural degeneration observed in MCI represents an early stage of Alzheimer's disease and other dementias (17), though heterogeneity in transitions from MCI is common. For example, not all individuals classified with MCI will develop Alzheimer's disease (18,19). Further, individuals who revert to normal cognitive functioning at some point during follow-up still remain at higher risk for progression to dementia (Koepsell & Monsell, 2012; Roberts et al., 2015). Further, cognitive status transitions can be challenging to capture given the timing of measurement occasions in longitudinal data collection.

Research aiming to investigate inter-individual differences in protective factors associated with heterogeneity in cognitive status transitions is timely due to recent advances in multi-state modeling (MSM), which allows simultaneous estimation of transitions through cognitive states while accounting for death, as well as estimation of life expectancy based on the hazard ratios estimated by the MSM. Additionally, MSM is desirable when the data are interval-censored, as is the case with panel data. That is, although cognitive impairment occurs as a process in continuous time, pre-scheduled interviews restrict the ability to measure the precise timing of changes. The current work investigates the impact of PA on cognitive status transitions, applying a coordinated analysis approach to fourteen longitudinal studies of aging

from seven affiliates of the Integrative Analysis of Longitudinal Studies on Aging and Dementia (IALSA) network (15). Coordinated analysis can protect against Type I and Type II errors by executing independent but conceptually identical analyses (to the extent possible) across multiple studies, permits a powerful basis to evaluate cross-country replicability, and facilitates accelerated accumulation of knowledge (15) (e.g., *see* Graham et al., 2020; Robitaille et al., 2018). The following research questions will be investigated: *To what extent does PA predict transitions between cognitive status categories? Do individuals who engage in more PA over the course of the study have longer life expectancies? Does a consistent pattern emerge across several studies of aging?* Based on previous research examining PA as a protective factor for cognitive functioning in older adulthood, we predict that individuals who engage in more PA will be less likely to transition to mildly and severely impaired cognitive status categories, as well as death, and will have longer life expectancies than individuals who engage in less PA.

Methods

Studies

Data were drawn from longitudinal studies affiliated with the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) network. Study selection was based on availability of repeated measurement of cognitive functioning and PA, as well as availability of an associated data analyst proficient in executing multistate modelling. One of these studies (SHARE; 16) includes data collected independently from 28 countries; studies that met eligibility (N=8; eligibility criteria listed in Supplementary Text 1) were therefore analyzed independently, making a total of fourteen longitudinal studies included in the current project. Baseline characteristics from each study are presented in Table 1, with additional demographic information presented in Supplemental Table 1. Given that transitioning to a cognitively

impaired state during the years of study follow-up is relatively rare for individuals who were less than 60 years old at baseline, only participants who were 60 years or older at baseline were included in the analysis. Eligibility also required individuals with complete demographic information and measurement of cognition at two or more occasions. Age at death was used to identify individuals who died during the study and when a known death date occurred after completion of the study. Ethical approval for each study was granted by governing research committees. All participants provided informed consent. The following is a list of contributing studies. Study details are included in Supplementary Text 1.

German Study on Ageing, Cognition, and Dementia (AgeCoDe) (17) (Germany).

Einstein Aging Study (EAS) (18) (United States of America).

Rush Memory and Aging Project (MAP) (19) (United States of America).

Longitudinal Aging Study Amsterdam (LASA) (20) (the Netherlands).

Health and Retirement Study (HRS) (21) (United States of America).

English Longitudinal Study of Aging (ELSA) (22) (United Kingdom).

Survey of Health, Ageing and Retirement in Europe (SHARE) (16). Countries with six or more waves of data and clear delineation of cognitive states were included in the current analysis: Austria, Belgium, Denmark, France, Germany, the Netherlands, Sweden, and Switzerland.

Measures

Each study involved an extensive battery of measures. We did not coordinate based on the lowest possible denominator (i.e., only using measures that were identical between studies); instead, we aimed to maximize available data to preserve the strengths of studies (e.g., clinical diagnosis > MMSE > summed cognitive test scores).

Cognitive Status Categories. Detailed operational definitions of cognitive status categories across studies are included in Supplementary Text 2. Formal clinical diagnoses of MCI and dementia were used for AgeCoDe, EAS and MAP. Cut-off scores on the Mini Mental State Examination (MMSE) were used for LASA. The Telephone Interview for Cognitive Status (TICS; 23)was used for HRS.

For ELSA and SHARE, select cognitive tests were summed, and study specific z-scores based on -2 and -1.5 standard deviations (SDs) below the study norm at baseline were used to operationalize severely and mildly cognitive status categories, respectively. For LASA, HRS, ELSA and SHARE, operationalization of cognitive status was used to determine suggestive rather than clinical diagnosis of MCI and dementia (i.e., based solely on cognitive functioning, not criteria for clinical diagnosis).

Physical Activity. To maximize available data while still allowing comparability between studies, and to characterize PA on a single scale, two transformations were executed to compute continuous PA variable representing intensity and frequency of PA at each measurement occasion. The first transformation utilized the Metabolic Equivalent of Task (MET) method developed by the Compendium of Physical Activities (24,25) to assign each PA item an intensity score, in which more vigorous activities are assigned higher values (e.g., walking=3; swimming=5; cycling= 6). The Compendium approach enhances comparability of self-report PA measures across studies by providing quantification of energy cost of common physical activities (24). The second transformation calibrated the reported frequency to represent approximate weekly engagement in PA. Thus, the PA variable represents *PA intensity units per week* (e.g., 15 units is reflective of approximately 150 minutes of moderate PA per week). Supplementary Table 2 lists assigned MET scores and frequency transformations across studies, while

Supplementary Text 3 provides detailed operational definitions. Based on the intraclass correlation coefficient (ICC; Supplementary Table 1), PA was highly heterogeneous at the within-person level over time, which justifies entering the variable into the multistate models as a time-varying covariate.

Covariates. Sex was included as a dichotomous variable (male as the reference group). Age was measured in years and centered at the baseline mean of each study. Due to the response options provided in the original survey, education was operationalized differently between studies (see Supplementary Text 4). For most studies, education was measured in years, centered at the value which indicates completion of high-school. For AgeCoDe, education was dummy coded into three categories representing compulsory schooling, high school, and post-secondary education. For ELSA, education was dichotomized and entered into models uncentered, indicating up to a high school education. An overall chronic conditions variable, computed as a count, was included to control for reduced PA due to health. See Supplementary Text 5 and Supplementary Table 3 for differences in inclusion and ascertainment of chronic conditions between studies.

Statistical Analysis

Multi-State Survival Modelling. A coordinated analysis approach was applied to allow independent analysis at the level of the individual study by applying the same analytic models to variables representing the same construct. Multi-state modeling (MSM; 26) was used to assess cognitive status transitions, aligned according to chronological age. While Cox regression models allow modeling of one transition (e.g., 13), MSM provides the opportunity to simultaneously model transitions between multiple cognitive status categories, and examine the impact of factors associated with each transition. A four state model was applied (State 1 = non-impaired cognitive functioning; State 2 = mildly impaired cognitive functioning; State 3 =

severely impaired cognitive functioning; State 4 = death). See Figure 1 for a representation of the four-state model. The MSM package (27) for R was used to estimate multistate survival models, which applies the general purpose optimization; the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method of algorithm was applied to optimize functioning. As PA was the main focus of these analyses, time-varying PA was included on all forward and backward transitions. To prevent numerical problems, the PA variable was scaled in some cases (e.g., the range was constrained by dividing PA values by 15); however, scaling does not impact significance of the hazard ratios (HR). Covariates (age, sex, education and chronic conditions) were included as covariates on forward transitions. For most studies (Age-CoDe, MAP, HRS, ELSA, Austria, Denmark, Germany, and Switzerland) with few individual backwards transitions, the effect of covariates were excluded from these backward transition estimates to simplify the model estimation. Given that transitioning from clinically diagnosed dementia back to mildly impaired cognitive functioning is rare (and often due to initial misdiagnosis), the transition from dementia to MCI was not modelled in studies that included clinical diagnoses (AgeCoDe, EAS, and MAP). For all other studies, in which cognitive status categories were operationalized based on cognitive tests, models included the possible backward transition from severely to mildly impaired cognitive functioning.

Life Expectancies. To complement the MSM analyses and provide a practical estimation of the impact of PA on mortality, total life expectancies (LEs) were estimated, conditional on age, using the elect package in R (28). The package fits a multinomial regression model using the transition probabilities estimated by the MSM for time-invariant covariates (besides age); therefore, the within-person average of the PA measure across all available occasions was computed, which is representative of an individual's overall level of PA compared to one

measurement occasion (29, 30), and entered into this second set of multi-state models as a time-invariant (rather than time-varying) variable for the LEs analysis. Across studies, LEs were estimated for male and female participants, for individuals at 70 and 80 years of age, at a high-school education or less no chronic conditions, and at three different levels for PA. American guidelines for PA recommend that, at minimum, older adults should engage in 150-300 minutes of moderate PA or 75-150 minutes of vigorous PA per week (31). Therefore, we translated the "PA intensity units per week" to reflect a sedentary lifestyle (i.e., 0 minutes/week), as well as approximately the lower (approx. 150 minutes) and upper (approx. 300 minutes) recommendations of minimum weekly engagement in moderate PA.

Meta-Analysis. To provide an overall effect size for the effect of PA on each transition, as well as pooled LEs, meta-analytic techniques were executed in R using the Metafor (32) package, in which studies with more precise standard errors are assigned more weight. A random effects approach was chosen, as the goal was to investigate the average true effect in the larger population of studies. Separate meta-analyses were run for each transition to account for the different nature of the effect sizes (e.g., normal cognition to death vs. normal cognition to mild impairment) as well as differences in prevalence of each transition. In order to facilitate interpretability, all HRs were scaled to indicate approximately 150 minutes of PA per week; however, given the between-study differences in PA variables, the computed meta-analysis effect size for each transition is intended to indicate direction and significance of engaging in more PA. The Hartung-Knapp (HK) method for random effects (33) was applied, which uses a refined estimator of variance and results in adequate error rates (34), particularly when there is heterogeneity in precision between studies (35).

Results

Given the emphasis of this project, we focus on the results regarding the impact of PA on transitions. Results regarding the covariates (i.e., age, sex, education and chronic conditions) are reported in Supplementary Table 4. The reported hazards ratios (HRs) and confidence intervals (CIs) reflect the effect of engaging in approximately 150 minutes of moderate PA per week on transitions between cognitive states. Although the magnitude of the estimated HR would change depending on the way in which PA is scaled, the direction and significance of the impact of PA on each transition remains constant (e.g., for 1 or 15 intensity units of PA per week).

Multi-State Survival Models with Physical Activity as a Time-Varying Covariate

The overall meta-analytic estimates (see Figure 1) indicate that more PA was associated with a significantly decreased risk of transitioning from non-impaired cognitive functioning to both mildly impaired cognitive functioning (HR=0.932; CI's=0.876, 0.991) and death (HR=0.657; CI's=0.595, 0.725). These results indicate a protective effect of PA, particularly for preventing death, and, to a lesser extent, prior to onset of cognitive impairment. In addition, the meta-analysis revealed that more PA was associated with a marginally significant (HR=0.995; CI's=0.911, 1.000; $p = 0.05$) decreased risk of transitioning from mildly impaired to severely impaired cognitive functioning; likewise, more PA was associated with a significant increased likelihood of transitioning backward from severely impaired to mildly impaired cognitive functioning (HR=1.061; CI's=1.012, 1.112). Together, these results indicate that PA may also be protective after onset of cognitive impairment. The meta-analytic results were mostly consistent with the individual study results, though there was some heterogeneity between studies. Hazard ratios and 95% confidence intervals (CIs) of the effect of PA specified as a time-varying covariate on transitions between states for each study are presented in Table 2.

The proportion of true variability of the effect of PA across studies relative to the total variability in observed effects was negligible ($I^2 = 0\%$) for the majority of transitions (6 out of 7), indicating relatively consistent estimates between studies. In contrast, for the effect of PA on the transition from non-impaired cognitive functioning to death, the relative proportion of true variability was substantial ($I^2 = 99.98\%$), indicating considerable heterogeneity that is likely due to sample specific characteristics, such as average age at baseline and targeted sample (e.g., EAS aimed to recruit healthy older adults). Further, the percentage of individuals who transitioned to death was highly heterogeneous between studies (9.5% in SHARE's Switzerland - 73.5% in LASA), mostly as a function of between sample differences in year of baseline measurement and mean age. The pooled, meta-analytic HRs (95% CIs) for the effect of approximately 150 minutes of PA per week on each transition are depicted in Figure 1.

Overall Life Expectancies

Estimated LEs are presented in Table 3 for 70 year olds and Table 4 for 80 year olds. Pairwise comparisons of the pooled LEs for approximately 0, 150 and 300 intensity units of PA revealed a positive linear effect of PA. Meta-analytic results indicate that, irrespective of sex or age, individuals who engage in approximately 300 minutes of PA per week live significantly longer than individuals who engage in approximately 150 minutes, and those individuals live significantly longer than individuals who do not engage in PA. Study-level results were consistent with meta-analytic results in all studies except LASA. The difference could be due to a combination of study-level and cultural differences; specifically, LASA has a very high mortality rate (73.5%) due to long-term follow-up, which may improve estimation of mortality. Further, participants in LASA were instructed to not include walking or bicycling for transportation purposes when they were completing the PA questionnaires, as these activities are

considered common daily activities in The Netherlands (not considered PA) (36). However, walking/cycling is likely to have similar physical benefits despite the purpose, which may contribute to variability in LASA's PA variable (i.e., measurement error). Supplementary Table 5 presents the HRs and 95% CIs for the multi-state models that the LEs are based on.

Discussion

Based on independent analysis of 14 longitudinal studies (total N = 52,039), our results indicate that engaging in more PA in older adulthood is associated with a decreased risk of mortality, controlling for age, sex, education, and chronic conditions. Meta-analytic results revealed that more PA was significantly associated with a decreased risk of transitioning from non-impaired cognitive functioning to mildly impaired cognition. Together, these results provide strong evidence for the importance of engaging in PA throughout older adulthood, particularly prior to onset of cognitive impairment. The meta-analytic results also revealed that more PA is associated with a decreased risk of transitioning from mildly impaired to severely impaired cognitive functioning, indicating that PA is also important after onset of impairment. For the 11 studies in which cognitive stateu wsa operationalized based on MMSE or cognitive task scores (i.e., not formal diagnoses), we modelled the backward transition from severely to mildly impaired cognition. The meta-analytic summary indicated that more PA was significantly associated with an increased likelihood of transitioning backwards, suggesting that engaging in more PA at the severely impaired stage may contribute to diminishing the symptoms that exacerbate poor cognitive performance. Alternatively, these results may indicate that individuals who are still able to engage in PA may have relatively better cognitive performance, and thus are more likely to perform below the cut-off for severe impairment at follow-up visits.

More PA was also associated with a reduced risk of transitioning forward through cognitively impaired status categories (e.g., from 2-3, and 3-4) in several individual studies (see Table 2). Due to fewer individuals with impaired cognitive status (compared to non-impaired), the power to detect these effects is more limited. Further, participants are more likely to drop out of a longitudinal panel study after onset of cognitive impairment (37). Although death data were ascertained via national death records in many of the studies, observing the transition to severely impaired cognition prior to death would be impossible in the case of attrition at the stage of mildly impaired cognitive functioning. Overall, the results point to a protective effect of PA after the onset of cognitive impairment; however, heterogeneity between studies and uncertainty in the pooled estimates indicates a less robust association.

Investigation of modifiable factors that contribute to transitioning back to non-impaired cognitive functioning are critical, as pharmacological solutions administered at the MCI stage tend to merely slow, rather than reverse, progression of cognitive impairment (). Our findings do not indicate that individuals who engaged in more PA are more likely to transition from mildly impaired back to non-impaired cognitive functioning; however, several factors may have impacted these results. For the current project, the timing of measurement occasions, which range from annually (EAS) to every three years (LASA), may limit the ability to capture cognitive status transitions that occur between measurement intervals. Indeed, Koepsell and Monsell (2012) found that 16% individuals with MCI (N=3020) revert back to non-impaired cognitive functioning approximately 1 year later, but that those individuals are also much more likely to retransition back to impaired cognitive states at later occasions. Further, in addition to other lifestyle characteristics (e.g., social and cognitive engagement), PA may contribute to cognitive reserve (Cheng, 2016). An individuals' accumulation of cognitive reserve may then

differentially impact the likelihood of cognitive status transitions; that is, once an individual has transitioned to mildly impaired cognition, engaging in more PA may no longer have the power to protect against cognitive decline. Thus, the intersection of PA and cognitive reserve may contribute to more variability in the impact of PA on transitions from mildly impaired cognitive status.

In recent years, the importance of knowledge mobilization has been gaining momentum. Researchers are encouraged to advocate for strategies that promote healthy aging by providing clearly defined recommendations (e.g., 40), especially in the form of specific health behaviours recommended for older adults (e.g., 150 minutes of moderate PA per week) (41). Indeed, based on previous literature, medical professionals are encouraged to consider promoting and even prescribing PA to their patients as a cost-effective approach to improve longevity and well-being (Jordan et al., 2018).Though the current project is based solely on longitudinal survey data, our findings contribute to the evidence for mechanisms of action through which improved outcomes may occur. Along with a myriad of existing research studies, in addition to national guidelines recommending PA as a preventative cure, the current coordinated analysis provides additional evidence for the importance of PA for improved cognitive outcomes and increased healthspan. Supplementary Figure 1, developed in collaboration with the Alzheimer Society of British Columbia, Canada, is an infographic summarizing the current research using graphics and easy-to-understand language. Medical professionals and interested readers are encouraged to print and post the poster in their offices in an effort to mobilize knowledge.

The current work is unable to make causal inferences based on observational data because we cannot exclude the possibility of a third, unmeasured variable causing changes in both cognitive functioning and PA, or reverse causation. Recent work (43,44) found no evidence

for an association of PA with dementia when PA is assessed more than 10 years prior to dementia onset, leading the researchers to posit that the relationship between PA and conversion to dementia may be due to reverse causation; namely, the prodromal phase of dementia may be characterized by a reduction in PA, such that increased PA does not cause less cognitive impairment, but less cognitive decline causes more PA. We believe that our results are not completely consistent with this reasoning. If decline in PA is a consequence of the dementia process (i.e., a marker of prodromal dementia), one would expect a strong association of PA in the transition from mildly impaired to severely impaired cognitive functioning because a large proportion of these participants (though not all) are likely to eventually transition to severe cognitive functioning. In contrast, one would expect a weaker effect in the transition from non-impaired to mildly impaired cognitive functioning because the non-impaired state includes, proportionally, fewer participants who will eventually transition to mildly impaired cognitive functioning. However, we observe the opposite pattern of results (i.e., a stronger effect of PA for the transition from non-impaired to mildly impaired cognition compared to the transition from mildly to severely impaired cognition, based on parameter estimate and p-value). Future research applying interventional designs should explore whether changes in PA are causal for changes in cognition on time scales shorter than 10 years.

Strengths, Limitations and Future Directions

Coordinating at the lowest possible denominator is common when coordinating analyses, but such an approach may disregard important qualities of a study. For this coordinated analysis, we aimed to maximize available data, while still allowing comparability between studies. For example, although EAS, MAP and AgeCoDe included administration of the MMSE and other cognitive tasks, we used formal diagnosis of MCI and dementia, which provides a more fine-

grained and precise estimate of cognitive status. Thus, this project represents *conceptual* replications rather than strict replications given between-study heterogeneity in study characteristics (e.g., frequency and timing between measurement occasions, country of origin) and operational definition of constructs (e.g., differences in measurement of cognitive functioning, PA, education, and chronic conditions). Between-study differences may be considered a limitation, particularly because the quality of PA variables and variables used to operationalize cognitive states varied between studies. However, between-study results were mainly consistent despite these differences, and heterogeneity in the key features of studies reinforces the implications of consistent results in a coordinated analysis (15).

Further, by characterizing PA on a single scale, our approach does not allow differentiation between PA intensity and frequency. However, given model complexity, computation of a single PA variable for each study was important to minimize included variables. This approach facilitated reporting and interpretation of results (which is particularly important when applying a coordinated analysis approach) and allowed greater comparability between studies. Future research differentiating the impact of PA frequency and intensity on cognitive status transitions may provide a more fastidious account of the benefits of PA. Relatedly, given the computational complexity of MSM, we were limited in the number of covariates that could be included in the models. Adjusting for additional covariates (e.g., depressive symptoms, pain, APOE status, functional limitations), would have strengthened the current project.

Computation and centering of values for the dependent and independent variables required several researcher decisions. Many of these decisions (e.g., statistical plan, covariates to be included in models) were pre-registered on December 4, 2018 on the Open Science

Framework (URL: https://osf.io/6t3sk/). Three specific aspects of the pre-registration were slightly modified: 1.) We originally planned to use cut-off scores on the MMSE, TICS and summed cognitive scores to operationalize cognitive states, but later decided to maximize available data wherever possible, such that incident formal diagnoses were used when available in order to highlight the strengths of individual studies, 2.) One study (OCTO-Twin) was not included because the available measurement of PA did not allow computation of a continuous PA score, and 3.) We originally planned to fit multi-state models for the life expectancies analysis using baseline PA, but later decided to use the average within-person PA score, as this value is more indicative of an individual's overall level of PA compared to one measurement occasion at an arbitrary time in the life span (i.e., "baseline"). We did not, however, fit the models using MMSE in the studies that also had formal diagnoses, or in the excluded study, or using baseline PA; therefore, we were not confronted with the opportunity to select the more "appealing" results. In addition, the current analyses were quite complicated, and therefore, only the main features of the analyses were pre-registered. For example, we decided to estimate life expectancies based on the minimum and maximum values of the American Physical Activity Standards after reading the 2018 Physical Activity Guidelines Advisory (31). Relatedly, all PA measures were self-report based on typical PA engagement, which may result in social influence bias or retrospection bias. Further, our analyses could not explicitly identify the level or duration of PA that is most beneficial (e.g., we estimated that each "time" or "day" that an individual reported engaging in PA was approximately equivalent to 50 minutes per session). Additionally, these analyses did not differentiate differences in dementia (e.g., Alzheimer's disease versus vascular) and MCI (e.g., aMCI versus naMCI) diagnoses. Future research using objective measures of PA (e.g., accelerometers), examining the impact of PA on transitions to different

types of dementia and MCI, and applying experimental or longitudinal measurement burst designs would improve our understanding of the impact of PA on cognition. Specifically, given that individuals who are exercising in late life are likely continuing an exercise habit initiated earlier in the life span, parallel process LGM examining trajectories of PA and cognitive functioning from midlife into older adulthood may provide the opportunity to examine individual differences in the importance of PA onset and maintaining PA.

Multi-State Survival Modeling provides a powerful analytic approach for discriminating the effect of PA at different stages of cognitive impairment, and these analyses highlight the importance of engaging in PA throughout older adulthood, and especially before onset of cognitive impairment. For example, although latent growth modeling (LGM) provides the opportunity to estimate intra-individual change and variation over time (e.g., within-person change in cognition), LGM typically assumes that the effect of the covariate (e.g., PA) is equal across the entire trajectory. That is, LGM assesses the effects of PA on continuous cognitive decline (i.e., unless the PA variable is entered as a time-varying covariate, the models are unable to determine the relative importance of PA through progression of cognitive impairment) making it harder to translate into clinical practice, whereas a MSM approach provides the opportunity to show when PA is most critical.

The meta-analytic pooled HRs indicated that the effect of PA was marginally significant for all transitions except the transition from non-impaired cognition to death (see Figure 1). With effects being drawn from only 11-14 independent studies, power to detect an effect may have been limited. With more individual studies included in this coordinated analysis, we may have had more power to meta-analyze study-level moderators (e.g., differences between operational definitions of cognitive status). Additionally, some of the effect sizes and associated confidence

intervals, particularly in the studies from SHARE, were imprecise, which is likely a function of few individual transitions between cognitive status categories. For example, across studies, the most recent baseline interviews were conducted in SHARE and AgeCoDe in 2003, and baseline age in SHARE is approximately 10 years younger than AgeCoDe, resulting in fewer instances of impairment. However, study effect sizes were weighted based on standard error (i.e., more precise studies were given more weight) for the meta-analysis; therefore, the pooled results were likely not strongly impacted by imprecise estimates. Furthermore, consideration of the context is important. Given the prevalence of cognitive decline in older adulthood, identification and further understanding of factors that may protect against cognitive aging are imperative. Existing literature documents a limited number of these factors, and although this synthesis is unable to make any causal determinations, PA *is* a modifiable lifestyle factor. Together, these considerations imply that the reduced risk associated with more physical activity should be seen as meaningful, despite being somewhat small. Future research examining PA across the entire lifespan (rather than > 60 years) may have the opportunity to examine potential critical periods of when PA may be most protective.

Conclusions

The consistency of results from 14 longitudinal studies provides strong evidence for the importance of engaging in PA throughout older adulthood. In addition to improving our understanding of the relationship between PA and transitions between cognitive status categories and death, as well as the feasibility and strengths of the coordinated analysis approach, this research provides evidence and basis for motivating individuals to engage in PA across the lifespan, and also for physicians to consider prescribing PA to their older patients.

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Table 1. Population Characteristics at Baseline for Each Study

Sample	Age-CoDe	EAS	MAP	LASA	HRS	ELSA	SHARE (Austria)	SHARE (Belgium)	SHARE (Denmark)	SHARE (France)	SHARE (Germany)	SHARE (Netherlands)	SHARE (Sweden)	SHARE (Switzerland)
N	2706	821	1428	2386	16135	5383	3306	3464	2370	3385	3224	1790	3525	2116
Age (SD)	81.73 (3.50)	79.34 (5.40)	80.52 (6.44)	70.23 (7.53)	71.42 (7.54)	70.09 (7.28)	70.51 (7.45)	71.28 (7.84)	70.75 (7.72)	71.75 (8.15)	69.92 (6.97)	69.94 (7.36)	71.05 (7.78)	70.77 (7.64)
Educ C	1*	12	12	9	12	0*	9	12	12	10	12	10	11	8
Female: n; %	1758; 65.0%	511; 62.2%	1010; 70.7%	1271; 53.2%	9442; 58.5%	2525; 46.9%	1900; 57.5%	1865; 53.8%	1262; 53.2%	1925; 56.9%	1586; 49.2%	898; 50.2%	1812; 51.4%	1094; 51.7%
Male: n; %	948; 35.0%	310; 37.8%	418; 29.3%	1115; 46.7%	6693; 41.5%	2858; 53.1%	1406; 42.5%	1599; 46.2%	1108; 46.8%	1460; 43.1%	1638; 50.8%	892; 49.8%	1713; 48.6%	1022; 48.3%
Baseline Cognitive State: n; %.														
State 1	2081; 77.3%	692; 84.3%	870; 61%	1717; 72.0%	14525; 90.0%	4844; 90.0%	3084; 93.3%	3196; 92.3%	2166; 91.4%	3145; 92.9%	2996; 92.9%	1655; 92.5%	3284; 92.3%	1964; 92.8%
State 2	544; 20.2%	126; 15.4%	458; 32.1%	574; 24.0%	1305; 8.1%	326; 6.1%	130; 3.9%	184; 5.3%	119; 5.0%	146; 4.3%	140; 4.3%	86; 4.8%	160; 4.5%	87; 4.1%
State 3	67; 2.5%	3; 0.4%	100; 7.0%	116; 4.9%	309; 1.9%	139; 2.6%	92; 2.8%	84; 2.4%	85; 3.6%	94; 2.8%	88; 2.7%	49; 2.7%	111; 3.1%	65; 3.1%
Deaths overall	1730; 63.9%	138; 16.8%	1050; 73.5%	1754; 73.5%	5931; 36.8%	1202; 22.3%	374; 11.31%	502; 14.5%	473; 20.0%	444; 13.1%	242; 7.5%	223; 12.5%	603; 17.1%	200; 9.5%

Note. AgeCoDe = German Study on Ageing, Cognition, and Dementia; EAS = Einstein Aging Study; MAP = Memory and Aging Project; LASA = Longitudinal Aging Study Amsterdam; HRS = Health and Retirement Study; ELSA = English Longitudinal Study of Aging; SHARE = Survey of Health, Ageing and Retirement in Europe; Age = Mean age at baseline; SD = Standard Deviation; Educ C = centering value used for education; State 1 = Non-impaired cognitive functioning; State 2 = Mildly impaired cognitive functioning; State 3 = Severely impaired cognitive functioning; MMSE=Mini Mental State Examination; TICS = Telephone Interview for Cognitive Status; *See Supplementary Text 3 for explanation of coding of education for AgeCoDe and ELSA.

Table 2. Hazard ratio and 95% Confidence Interval for the effect of Physical Activity as a Time-Varying Variable on Transitions of Older Adults through States of Cognitive Functioning for Each Study

Sample	Age-Code	EAS	MAP	LASA	HRS	ELSA	SHARE (Austria)	SHARE (Belgium)	SHARE (Denmark)	SHARE (France)	SHARE (Germany)	SHARE (Netherlands)	SHARE (Sweden)	SHARE (Switzerland)
Transition	Hazard ratios (95% CIs)													
State 1-State 2	0.996 (0.992-1.001)	**0.904 (0.820, 0.997)**	0.944 (0.875, 1.019)	1.019 (0.986, 1.053)	**0.997 (0.995, 0.999)**	**0.984 (0.978, 0.990)**	**0.963 (0.943, 0.982)**	**0.636 (0.516, 0.783)**	**0.965 (0.950, 0.980)**	0.805 (0.628, 1.033)	**0.982 (0.967, 0.998)**	0.780 (0.581, 1.047)	0.989 (0.976, 1.003)	**0.691 (0.553, 0.864)**
State 1-State 4	**0.974 (0.965-0.982)**	0.879 (0.706, 1.094)	**0.398 (0.266, 0.595)**	**0.355 (0.261, 0.479)**	**0.908 (0.896, 0.920)**	**0.916 (0.894, 0.940)**	**0.940 (0.909, 0.972)**	**0.524 (0.415, 0.663)**	**0.962 (0.941, 0.984)**	**0.447 (0.329, 0.607)**	**0.902 (0.823, 0.988)**	**0.398 (0.618, 0.257)**	**0.953 (0.933, 0.973)**	**0.622 (0.413, 0.938)**
State 2-State 1	1.001 (0.996-1.006)	**0.895 (0.802, 0.998)**	1.075 (0.994, 1.162)	0.989 (0.947, 1.032)	**1.003 (1.000, 1.006)**	1.007 (0.999, 1.015)	1.017 (0.994, 1.040)	0.860 (0.669, 1.105)	1.013 (0.992, 1.034)	**1.514 (1.093, 2.097)**	1.000 (0.978, 1.023)	1.299 (0.877, 1.936)	1.003 (0.984, 1.023)	0.913 (0.670, 1.244)
State 2-State 3	**0.984 (0.978-0.991)**	0.903 (0.737, 1.106)	0.951 (0.842, 1.074)	**0.910 (0.848, 0.975)**	**0.993 (0.988, 0.997)**	0.998 (0.988, 1.008)	1.028 (0.994, 1.064)	**0.695 (0.484, 0.999)**	0.998 (0.970, 1.026)	0.958 (0.654, 1.403)	1.014 (0.988, 1.041)	1.097 (0.683, 1.763)	0.996 (0.938, 1.056)	4.754 (0.807, 28.014)
State 2-State 4	1.011 (0.997-1.026)	1.026 (0.228, 4.622)	1.124 (0.917, 1.378)	1.029 (0.973, 1.09)	**1.011 (1.007, 1.014)**	**1.069 (1.000, 1.142)**	0.470 (0.086, 2.57)	0.255 (0.028, 2.324)	0.988 (0.955, 1.022)	1550.077 (0.015, 1.620e8)	0.842 (0.643, 1.103)	0.301 (0.001, 75.051)	0.864 (0.746, 1.000)	0.782 (0.532, 1.150)
State 3-State 2	1.000		1.110 (0.949, 1.275)	**1.082 (1.004, 1.167)**	1.006 (0.999, 1.014)	1.011 (0.998, 1.025)	1.010 (0.974, 1.048)	0.962 (0.574, 1.612)	**1.054 (1.018, 1.092)**	**1.696 (1.021, 2.819)**	1.030 (0.997, 1.063)	0.499 (0.003, 89.954)	1.041 (0.933, 1.161)	5.217 (0.878, 31.000)
State 3-State 4	**0.991 (0.983-0.999)**	0.946 (0.703, 1.273)	0.837 (0.683, 1.025)	**0.879 (0.800, 0.967)**	**0.991 (0.985, 0.997)**	0.991 (0.978, 1.004)	**1.038 (1.000, 1.078)**	0.867 (0.529, 1.421)	**0.943 (0.906, 0.982)**	0.711 (0.460, 1.098)	**1.026 (1.003, 1.050)**	1.386 (0.752, 2.554)	0.984 (0.964, 1.005)	0.055 (0.001, 2.685)

Note. AgeCoDe = German Study on Ageing, Cognition, and Dementia; EAS = Einstein Aging Study; MAP = Memory and Aging Project; LASA = Longitudinal Aging Study Amsterdam; HRS = Health and Retirement Study; ELSA = English Longitudinal Study of Aging; SHARE = Survey of Health, Ageing and Retirement in Europe; State 1 = Non-impaired cognitive functioning; State 2 = Mildly impaired cognitive functioning; State 3 = Severely impaired cognitive functioning; State 4 = Death; bold = $p < 0.05$.

Table 3. Life expectancies for male and female participants at age 70 with up to a high school education and no chronic conditions and physical activity values based on American Standards

Sample	Age-Code*	EAS	MAP	LASA	HRS	ELSA	SHARE (Austria)	SHARE (Belgium)	SHARE (Denmark)	SHARE (France)	SHARE (Germany)	SHARE (Netherlands)	SHARE (Sweden)	SHARE (Switzerland)	Overall Pooled Estimate
Life expectancies in years (95% CIs) for a 70 year old															
Male, PA (0 mins)	7.90 (5.01, 8.95)	15.12 (9.50, 16.86)	9.77 (8.40, 10.87)	9.73 (8.84, 10.84)	6.90 (6.43, 7.43)	10.77 (9.43, 12.14)	4.87 (2.20, 6.17)	11.90 (2.94, 13.49)	8.50 (5.19, 10.35)	6.93 (3.98, 9.19)	7.53 (5.80, 11.01)	12.63 (6.05, 17.56)	11.07 (2.78, 13.28)	6.63 (3.95, 9.13)	9.82 (8.40, 11.24)
Male, PA (150 mins)	8.67 (5.46, 9.65)	16.86 (12.95, 18.37)	12.06 (10.68, 13.02)	9.65 (8.84, 10.67)	10.51 (9.98, 10.94)	15.48 (13.68, 16.02)	16.60 (9.07, 19.46)	15.53 (6.32, 16.60)	13.01 (8.93, 14.30)	15.22 (8.51, 16.63)	22.56 (16.57, 26.56)	17.20 (10.85, 23.34)	14.79 (4.74, 16.44)	14.86 (9.97, 16.74)	13.88 (12.45, 15.31)
Male, PA (300 mins)	9.47 (5.94, 10.43)	18.27 (14.14, 20.54)	13.54 (11.85, 14.90)	9.57 (8.81, 10.52)	11.76 (11.09, 12.41)	17.26 (15.13, 18.43)	19.37 (13.67, 23.13)	20.56 (13.65, 22.58)	16.26 (11.65, 18.94)	17.31 (4.75, 20.12)	20.71 (14.56, 26.65)	21.47 (13.73, 31.85)	18.89 (13.66, 21.24)	14.25 (8.39, 16.54)	15.19 (13.74, 16.64)
Female, PA (0 mins)	10.29 (8.28, 11.04)	16.70 (4.32, 19.12)	12.48 (11.34, 13.36)	11.42 (10.54, 12.24)	8.80 (8.33, 9.28)	13.61 (12.18, 14.99)	8.31 (3.63, 10.80)	12.64 (7.24, 15.64	9.69 (6.79, 12.20)	9.68 (5.71, 13.28)	13.20 (9.42, 16.36)	19.32 (10.69, 26.42)	7.65 (4.51, 12.13)	11.18 (5.46, 15.12)	12.66 (10.95, 14.38)
Female, PA (150 mins)	11.21 (9.09, 11.73)	19.20 (13.00, 22.03)	14.76 (13.52, 15.84)	11.34 (10.55, 12.25)	13.02 (12.45, 13.51)	18.87 (17.41, 19.60)	20.44 (11.32, 22.59)	17.19 (11.08, 19.82	15.25 (10.73, 17.36)	19.03 (6.75, 20.95)	23.61 (17.27, 26.72)	24.21 (14.82, 35.87)	16.70 (11.11, 18.26)	17.54 (10.92, 19.76)	16.63 (14.92, 18.34)
Female, PA (300 mins)	12.16 (9.96-12.71)	20.63 (14.08, 23.81)	16.06 (14.11, 17.26)	11.25 (10.51, 12.23)	14.50 (13.72, 15.12)	22.26 (19.52, 23.80)	20.19 (14.52, 26.29)	22.88 (8.16, 27.64)	20.41 (13.24, 23.25)	21.99 (5.33, 25.46)	22.53 (14.92, 29.00)	28.35 (18.40, 48.10)	21.42 (12.29, 23.78)	16.12 (11.65, 18.86)	18.09 (16.36, 19.81)

Note. AgeCoDe = German Study on Ageing, Cognition, and Dementia; EAS = Einstein Aging Study; MAP = Memory and Aging Project; LASA = Longitudinal Aging Study Amsterdam; HRS = Health and Retirement Study; ELSA = English Longitudinal Study of Aging; SHARE = Survey of Health, Ageing and Retirement in Europe; PA = Physical Activity; PA (0 mins) = Approximately 0 minutes of PA per week; PA (150 mins) = Approximately 150 minutes of PA per week; PA (300 mins) = Approximately 300 minutes of PA per week. *AgeCoDe centered at 76 (youngest participants at baseline).

Table 4. Life expectancies for male and female participants at age 80 with up to a high school education and no chronic conditions and physical activity values based on American Standards

Sample	Age-Code	EAS	MAP	LASA	HRS	ELSA	SHARE (Austria)	SHARE (Belgium)	SHARE (Denmark)	SHARE (France)	SHARE (Germany)	SHARE (Netherlands)	SHARE (Sweden)	SHARE (Switzerland)	Overall Pooled Estimate
Life expectancies in years (95% CIs) for an 80 year old															
Male, PA (0 mins)	5.90 (4.51, 6.64)	9.45 (6.38, 10.90)	5.73 (5.02, 6.42)	5.30 (4.76, 6.12)	4.87 (4.51, 5.33)	6.92 (6.89, 7.82)	3.91 (2.52, 5.63)	7.76 (3.51, 8.96)	5.36 (3.47, 6.60)	7.96 (5.84, 9.25	4.40 (3.16, 7.15)	8.14 (4.43, 11.52)	7.20 (3.91, 8.56)	4.44 (2.43, 6.63)	6.50 (5.56, 7.44)
Male, PA (150 mins)	6.52 (4.99, 7.20)	10.80 (8.21, 12.11)	7.05 (6.37, 7.63)	5.31 (4.80, 6.00)	8.40 (7.99, 8.66)	9.51 (9.31, 10.08)	11.15 (7.89, 13.34)	10.50 (6.42, 11.49)	8.76 (6.27, 10.05)	10.91 (7.46, 12.12)	15.26 (9.33, 19.03)	11.55 (7.55, 16.37)	9.45 (7.33, 10.69)	9.93 (7.20, 10.99)	9.23 (8.29, 10.18)
Male, PA (300 mins)	7.18 (5.42, 7.86)	11.92 (8.06, 13.46)	7.86 (6.86, 8.79)	5.25 (4.79, 5.87)	9.99 (9.57, 10.47)	9.97 (9.71, 11.06)	14.89 (11.44, 18.63)	14.48 (10.64, 16.54)	12.28 (8.20, 13.66)	11.70 (7.23, 14.80)	13.28 (7.44, 19.71)	14.63 (9.08, 24.38)	12.47 (10.72, 14.87)	9.77 (7.08, 11.56)	10.31 (9.34, 11.28)
Female, PA (0 mins)	7.96 (7.02, 8.46)	10.72 (6.61, 13.20)	7.60 (6.97, 8.18)	6.50 (5.88, 7.07)	6.28 (5.91, 6.62)	8.78 (8.73, 9.59)	6.58 (3.76, 8.46)	7.91 (5.22, 10.52)	6.02 (4.37, 7.95	10.21 (7.80, 11.58)	8.28 (5.67, 11.43)	13.87 (7.69, 19.69)	9.16 (7.11, 10.71)	8.05 (4.29, 10.87)	9.07 (7.79, 10.36)
Female, PA (150 mins)	8.72 (7.82, 9.15)	12.68 (9.51, 14.94)	8.96 (8.27, 9.63)	6.43 (5.83, 7.05)	10.20 (9.81, 10.49)	12.04 (11.83, 12.73)	13.85 (10.32, 16.12)	11.36 (9.00, 13.52)	10.41 (7.85, 12.12)	13.57 (9.39, 14.92)	15.89 (9.64, 19.12)	17.16 (10.57, 27.88)	11.88 (10.13, 13.60)	12.33 (8.98, 13.95)	11.46 (10.17, 12.75)
Female, PA (300 mins)	9.53 (8.57, 9.90)	13.86 (9.93, 16.18)	9.70 (8.59, 10.50)	6.36 (5.79, 7.02)	11.87 (11.45, 12.36)	14.49 (14.14, 16.00)	16.51 (12.51, 21.13)	15.95 (11.66, 21.03)	15.69 (8.62, 18.09)	15.27 (8.96, 18.68)	14.67 (7.32, 21.14)	20.18 (13.05, 39.59)	14.79 (11.93, 17.48)	11.76 (9.07, 13.69)	12.59 (11.27, 13.91)

Note. AgeCoDe = German Study on Ageing, Cognition, and Dementia; EAS = Einstein Aging Study; MAP = Memory and Aging Project; LASA = Longitudinal Aging Study Amsterdam; HRS = Health and Retirement Study; ELSA = English Longitudinal Study of Aging; SHARE = Survey of Health, Ageing and Retirement in Europe; PA = Physical Activity; PA (0 mins) = Approximately 0 minutes of PA per week; PA (150 mins) = Approximately 150 minutes of PA per week; PA (300 mins) = Approximately 300 minutes of PA per week.