Research Article

Physical Activity in Early- and Mid-Adulthood Are Independently Associated With Longitudinal Memory Trajectories in Later Life

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Abstract

Background: Physical activity (PA) in later life may reduce dementia risk, but little is known regarding long-term cognitive effects of PA that occurred earlier in adulthood or mechanisms underlying associations. PA patterns at different ages may independently contribute to dementia risk, which would implicate multiple critical periods for intervention. The current study tested whether retrospective reports of PA in early and mid-adulthood were independently associated with later-life longitudinal memory outcomes and whether associations were mediated by late-life cardiometabolic diseases.

Method: Participants comprised 5200 Health and Retirement Study Life History Mail Survey respondents. Latent growth curves estimated independent associations between retrospectively reported PA in early adulthood (age 18–29) and mid-adulthood (age 40–49) and 16-year episodic memory trajectories. Indirect pathways involving the maintenance of PA from early- to mid-adulthood and the influence of PA on later-life cardiometabolic diseases (hypertension, diabetes, and heart disease) were also estimated.

Results: PA in early- and mid-adulthood independently predicted higher initial memory level and slower memory decline in later life, respectively. Early-adulthood PA was indirectly associated with later-life memory level through higher mid-adulthood PA and lower rates of later-life hypertension, as well as with subsequent memory decline through higher mid-adulthood PA.

Conclusions: The current findings highlight the importance of PA throughout adulthood, such that initiating and/or maintaining exercise in early- or mid-adulthood may be protective for later-life cognitive health, and hypertension appears to represent a key mediator of these effects.

Keywords: Cognitive aging, Exercise, Hypertension, Resilience

Physical inactivity represents a modifiable risk factor for dementia in older adults (1). Estimates suggest that a 25% reduction in the prevalence of physical inactivity could prevent approximately 1 million Alzheimer's disease cases worldwide (2). Physical activity (PA) in older adulthood has been associated with better cognitive performance and reduced risk for dementia (3–7). A growing body of research suggests that PA across earlier periods of adulthood may confer later-life cognitive health benefits. Specifically, longitudinal studies using observational data show that greater physical fitness in early- (8) or mid-adulthood (9–11) is associated with lower later-life dementia risk. For instance,

a cohort study of adults followed for up to 42 years showed that low (vs high) physical fitness in early adulthood assessed using an in-person exercise test was associated with an approximately 2.5-fold increased risk for dementia (8). A separate population-based study comprising an older adult sample followed for 44 years showed that higher levels of self-reported PA in midlife was associated with reduced risk for dementia, with estimates varying by different dementia subtypes (11). Furthermore, a recent longitudinal study in adults aged 28–84 at baseline found that more self-reported PA at the initial assessment was associated with less decline in episodic memory scores 10 years later (12).

Because most previous studies of cognitive outcomes have examined PA during discrete periods in isolation (eg, early- or mid-adulthood) or continuously (eg, early- *throughout* mid-adulthood), less is known regarding the independence of associations between PA during different periods of adulthood (ie, early- vs mid-adulthood) and later-life cognitive health outcomes. One study found that PA during different periods of adulthood (ie, early- and mid-adulthood) may make independent contributions to later-life cognition (13). However, this study was restricted to women and included relatively crude measures of both PA (ie, a dichotomous variable reflecting any PA versus no PA) and cognition (ie, a single assessment using a dementia screening tool with limited sensitivity to earlier age-related declines). In contrast, a separate cross-sectional study showed that retrospectively reported PA during early- but not mid-adulthood was associated with better later-life global cognition measured at one timepoint, though this study comprised a small, regionally restricted sample of currently physically inactive participants (4). Additional evidence for independent effects of PA during early- and mid-adulthood may suggest multiple potential critical periods for intervention and point to the utility of developmentally tailored approaches to facilitate PA at these unique adulthood age periods. Independent effects of PA during early- and mid-adulthood would also help to refine predictive models of dementia risk, which presently show that physical inactivity in later life confers risk for dementia (1).

Importantly, long-term associations between adulthood PA and episodic memory *trajectories* remain unclear. One difficulty in evaluating associations between late-life PA and dementia risk relates to the potential for reverse causation. Specifically, cognitive declines in later life have been shown to precede functional declines (14) and reduce engagement in leisure activities such as PA (15). Indeed, progressive declines in everyday functional activities are characteristic of the preclinical or prodromal stage of dementia (16). Studies that estimate the effects of early- and mid-adulthood PA on trajectories of later-life episodic memory (ie, prior to potential disease-related changes in PA) and include time lags between the measurement of PA and cognition may be less prone to reverse causation bias than studies in which PA–cognition associations are investigated over a shorter period of time.

While a growing body of research has investigated mechanistic pathways linking later-life PA to concurrent cognitive performance, it is unclear whether the same mechanisms could underlie longer-term cognitive effects of PA that occurred earlier in adulthood. Cardiometabolic function may represent one potential mechanism underlying the association between later-life PA and cognitive health (17). Indeed, physical inactivity has been shown to negatively impact metabolic and cardiovascular functions, increasing risk of cardiometabolic diseases such as hypertension, (18) diabetes, (19), and heart diseases (20). Individuals with these diseases, in turn, have greater risk for dementia (21). Therefore, later-life cardiometabolic diseases may represent potential pathways linking the previously documented protective effects of PA patterns during various periods of adulthood on later-life cognitive health. Elucidating mechanisms underlying PA–cognition associations may reveal more precise targets of interventions at different stages of adulthood and potentially advance intervention efficacy.

The aims of the current study are 2-fold. First, to test whether early- and mid-adulthood PA are independent predictors of later-life memory trajectories (Aim 1). We hypothesized that there would be independent associations between more PA during both early- and mid-adulthood and higher later-life memory level, as well as slower subsequent memory decline (Hypothesis 1). Second, the current study aimed to examine pathways linking early- and mid-adulthood PA to later-life memory outcomes (Aim 2). Previous research suggests that

early-adulthood PA predicts mid-adulthood PA (22) and that mid-adulthood PA is associated with late-life cognitive health (11–13,24). Therefore, we hypothesized that positive associations between early-adulthood PA and later-life memory would be partially explained by continued PA in mid-adulthood (Hypothesis 2a). Finally, we hypothesized that associations between early- and mid-adulthood PA and memory would be partially explained by lower later-life prevalence of cardiometabolic diseases (ie, hypertension, diabetes, and heart disease) (Hypothesis 2b).

Method

Study Design and Participants

Data for the current study's analytic sample ($N = 5200$) are from the Health and Retirement Study (HRS). The HRS is a longitudinal cohort study of adults aged 51+ followed since 1992 (23). The HRS employs a national area probability sample of U.S. households, oversampling for Blacks, Hispanics, and residents of Florida. In 1998, the HRS began enrolling and conducting biennial interviews with participants from all age-eligible birth cohorts. In order to maintain its U.S.-representative sample of adults aged 51+, the HRS utilizes a steady-state panel design for recruitment in which a refresher sample is added every 6 years, which replenishes the sample with new participants from younger, now age-eligible, cohorts. The HRS study design and assessments are available online (<http://hrsonline.isr.umich.edu>).

In 2015, the HRS initiated a Life History Mail Survey, which included retrospective reports of early- and mid-adulthood PA (described below). Two mutually exclusive random subsamples of HRS participants were selected to participate in the Life History Mail Survey in either 2015 or 2017. Response rates were 58% and 74% for the 2015 and 2017 waves, respectively. In the current study, PA data from these random subsamples were combined to maximize sample size.

Longitudinal episodic memory scores were available for up to 9 biennial waves, corresponding to a maximum follow-up period of 16 years (1998–2014). Mediator and covariate data (described below) were obtained at each participant's first memory assessment (ie, participant-specific baseline or T1). Given the HRS sampling design, participants' baseline episodic memory assessment (T1) could correspond to 1998, 2004, or 2010.

To minimize the potential for reverse causation, we employed a time lag between the oldest possible age of retrospectively reported PA (age 49) and the youngest possible baseline age for inclusion in our analyses (age 55). Thus, HRS participants were included in the current study if they (a) were aged 55+ at T1, (b) completed the HRS Life History Mail Survey in 2015 or 2017 (from which PA data were obtained), and (c) had no missing sociodemographic data. Characteristics of the 5200 individuals included in the current study are provided in Table 1. All participants provided written informed consent, and all study procedures were approved by the University of Michigan institutional review board.

Measures

Episodic memory

Episodic memory was the outcome variable. Although processing speed and executive function are implicated in studies of PA and cardiometabolic diseases, the HRS has not routinely included measures of these cognitive domains. Therefore, episodic memory was selected as the cognitive performance measure because it is sensitive to age-related cognitive decline and is a well-documented primary determinant of dementia risk (24). In the HRS, episodic memory is

assessed biennially with a word list-learning task shown to have adequate validity (25), reliability (coefficient = .85), and measurement invariance across racial and ethnic groups (26).

Participants heard one of 4 randomly selected lists of 10 nouns, with varied lists used for 4 successive waves of data collection. Participants recalled the words immediately and after a 5-minute delay. Raw scores on the immediate and delayed recall trials were used to calculate *z*-scores using means and standard deviations from the current sample's T1 memory assessment. *Z*-scores were averaged into a composite to improve the reliability of the episodic memory outcome.

Physical activity

PA in early- and mid-adulthood were the exposure (independent) variables and were retrospectively reported as part of the Life History Mail Survey. Respondents separately rated single-items assessing the frequency of moderate and vigorous PA during early adulthood (ages 18–29) and mid-adulthood (ages 40–49). Thus, the study included a total of 4 PA responses, corresponding to 2 levels of activity (ie, moderate and vigorous) for the 2 age periods. Moderate PA was assessed with a question regarding the frequency of “physical activities that are **moderately energetic** such as walking for more than 30 minutes at a moderate pace, dancing, floor or stretching exercises?” Vigorous PA was assessed with the question “how often did you take part in or train for sports or activities that are **vigorous**, such as running or jogging, swimming, cycling, football, snow sports, aerobics or gym workouts, or tennis?” The Life History Mail Survey is publicly available online to registered users (<http://hrsonline.isr.umich.edu>). Items were coded on a 5-point scale from 0 (*Hardly ever or never*) to 4 (*Every day*). PA scores were computed separately by multiplying the frequency of PA with its estimated energy expenditure, expressed in metabolic equivalent (MET) values for both moderate (MET = 1.4) and vigorous (MET = 1.8) PA (27,28). PA for

the 2 age periods (ie, early- and mid-adulthood) was the sum of their respective moderate and vigorous MET-adjusted scores and were included simultaneously in all models.

Cardiometabolic diseases

Participants self-reported whether they had ever received a diagnosis of hypertension, diabetes, or heart disease from their physician (yes/no). Data were obtained at T1. These diseases were modeled simultaneously as independent mediators of associations between PA and memory trajectories.

Covariates

Covariates included age (years), sex/gender (with male as the reference category), race and ethnicity (with non-Hispanic White as the reference category), education (years), childhood socioeconomic status (SES; mother's highest education in years) (29), and birth cohort (with mid baby boomers as the reference category), which were all obtained at T1, as well as HRS Life History Mail Survey completion year (2015 or 2017, with 2015 as the reference category). These variables were included as covariates as they represent potential confounders of the relationships among PA levels, cardiometabolic diseases, and/or cognitive performance. Additionally, the number of memory assessments that participants completed was included as a covariate to minimize potential practice and retest effects. Sensitivity analyses included retrospectively reported childhood family financial status, with responses ranging from 1 (*Pretty well off financially*) to 3 (*Poor*).

Analytic Strategy

Statistical analyses were conducted using Mplus version 8. Memory trajectories were modeled using latent growth curve analysis and estimated with maximum likelihood. Time was parameterized as years from T1 (ie, participants' first memory assessment in 1998, 2004, or 2010). Participants had an average of 7.48 (*SD* = 2.50) memory assessments. The model estimated 2 latent outcome variables: initial memory level (intercept) and subsequent rate of change in memory over the 16-year follow-up period (linear slope).

To test Aim 1 (Figure 1), we estimated independent associations between the 2 exposure variables (ie, early- and mid-adulthood PA) and both memory intercept and slope, independent of covariates. Exposures and outcomes were regressed onto covariates. Early- and mid-adulthood PA were allowed to correlate. To test Aim 2 (Figure 2), we estimated direct and indirect effects of early- and mid-adulthood PA on memory intercept and slope through the 3 simultaneous cardiometabolic disease mediators (hypertension, diabetes, and heart disease), independent of covariates. In this model, memory intercept and slope were regressed onto both exposures and all 3 mediators, and all mediators were regressed onto both early- and mid-adulthood PA. In addition, mid-adulthood PA was regressed onto early-adulthood PA in order to clarify whether early-adulthood PA might impact later-life memory *through* its association with mid-adulthood PA (Hypothesis 2a), and mediators were allowed to covary. All exposure, mediator, and outcome variables were regressed onto covariates. Model fit was evaluated using established indices: comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). CFI > .95, RMSEA < .06, and SRMR < .05 were used to determine adequate model fit (30). This combination of model fit indices was selected because each individual statistic has advantages and disadvantages. CFI compares an estimated model

Table 1. Participant Characteristics

Variable	Mean (SD) or %	Sample Range
Age (years)	61.16 (5.56)	55–88
Education (years)	13.22 (2.70)	0–17
Female	58.1	
Maternal education ^a (years)	13.22 (2.70)	0–17
Race and ethnicity		
Non-Hispanic Black	15.80	
Hispanic (any race)	6.10	
Non-Hispanic “other”	2.20	
Non-Hispanic White	75.90	
Number of memory assessments completed	7.48 (2.51)	1–9
Year of Life History Mail Survey completion (% 2015)	63.20	
Early-adulthood physical activity (METs)	8.00 (4.35)	1.40–16.00
Mid-adulthood physical activity (METs)	7.35 (3.94)	1.40–16.00
Hypertension (% yes)	39.20	
Type 2 diabetes (% yes)	9.60	
Heart disease (% yes)	11.50	
Immediate recall score	6.18 (1.54)	0–10
Delayed recall score	5.12 (1.95)	0–10

Note: METs = metabolic equivalents.

^aMaternal education (years) was used to operationalize childhood socioeconomic status.

with a hypothetical null model, which may itself be inaccurate. RMSEA is an index of model discrepancy for degrees of freedom, which incorporates model complexity, though RMSEA usually improves with increasing sample sizes. Low SRMR suggests low model residuals but does not consider model complexity. When considered together, these 3 statistics reduce the likelihood of choosing a bad model (31).

Results

Participant characteristics are presented in Table 1. The first model quantifying independent associations between early- versus mid-adulthood PA and later-life memory outcomes (Aim 1) fit very well: CFI = .984, RMSEA = .020 (90% CI: .018–.022), SRMR = .022. As depicted in Figure 1, more PA in early adulthood was associated with higher later-life memory level but not subsequent memory change independent of mid-adulthood PA, whereas more PA in mid-adulthood was associated with slower later-life memory decline, but not initial memory level.

Pathways Linking Early- and Mid-Adulthood PA to Later-Life Memory Outcomes

The second model (Aim 2) incorporating a path from early- to mid-adulthood PA (Hypothesis 2a) as well as paths through the cardiometabolic mediators (Hypothesis 2b) fit very well: CFI = .985, RMSEA = .018 (90% CI: .016–.020), SRMR = .020 (Table 2).

Initial Memory Level

The association between more early-adulthood PA and higher initial memory level was partially mediated by mid-adulthood PA and hypertension. Specifically, more PA in early adulthood was associated with more PA in mid-adulthood, which in turn was associated with a lower prevalence of later-life hypertension, which in turn was associated with higher initial memory level (Figure 2). Early-adulthood PA was also directly associated with higher later-life initial memory level independent of mid-adulthood PA and all cardiometabolic mediators. In contrast, there was no direct effect of mid-adulthood PA on initial memory level independent of cardiometabolic diseases. There were no indirect effects of either early- or mid-adulthood PA on initial memory level through diabetes or heart disease. Although more mid-adulthood PA was independently associated with a lower prevalence of both later-life diabetes ($\beta = -0.057$, $SE = 0.019$, $p = .002$, 95% CI: -0.093 to -0.021) and heart disease ($\beta = -0.042$,

Figure 2. Schematic of the longitudinal mediation model of pathways linking early- and mid-adulthood physical activity to later-life memory outcomes. Solid lines indicate significant ($p < .05$) paths, and dotted lines indicate nonsignificant paths. Values shown are standard estimates (SEs). For simplicity, covariates are not shown.

$SE = 0.019$, $p = .023$, 95% CI: -0.079 to -0.006), neither of these cardiometabolic diseases were associated with concurrent memory level ($ps > .05$).

Rate of Memory Change

More PA in early adulthood was associated with less later-life memory decline indirectly through more PA in mid-adulthood. There was no direct effect of early-adulthood PA on later-life memory change independent of mid-adulthood PA. Furthermore, there were no indirect effects of either early- or mid-adulthood PA on later-life rate of memory change through any of the cardiometabolic mediators.

Sensitivity Analyses

First, maternal education was replaced with retrospectively reported childhood family financial status as the covariate to adjust for childhood SES. Patterns of associations persisted across models. Second, because low memory scores may bias reports of PA levels earlier in life and/or reflect prevalent dementia, analyses excluded participants whose T1 memory score was less than 2 SDs below the mean. Patterns of association in this restricted sample ($n = 4916$) were nearly identical to those observed in primary models.

Discussion

Findings of this U.S.-wide longitudinal study show independent associations between both early-adulthood (ages 18–29) and mid-adulthood (ages 40–49) PA and later-life memory outcomes and provide preliminary evidence about potential pathways underlying these associations. When considered as independent predictors (Aim 1), early-adulthood PA only predicted later-life memory level, while mid-adulthood PA only predicted subsequent memory decline. When considered in a mediation framework (Aim 2), early-adulthood PA showed an additional association with memory decline through mid-adulthood PA. With regard to cardiometabolic mediators, the positive associations between PA earlier in the adult lifecourse and later memory level appeared to be partially driven by later-life hypertension, but not diabetes or heart disease. In contrast, the positive association between early-adulthood PA and rate of subsequent memory decline appeared to be independent of these cardiometabolic conditions. Altogether, the current study suggests that early- and mid-adulthood may represent independent critical periods for engaging in PA and that the potential protective cognitive effects of PA at different periods of adulthood are only partially explained by later-life cardiometabolic diseases.

Figure 1. Schematic of the longitudinal prediction model showing independent early- and mid-adulthood physical activity associations with memory outcomes. Solid lines indicate significant ($p < .05$) paths, and dotted lines indicate nonsignificant paths. Values shown are standard estimates (SEs). For simplicity, covariates are not shown.

Table 2. Standardized Results From the Mediation Model

	Initial Memory Level			Rate of Memory Change		
	Estimate (SE)	95% CI	<i>p</i>	Estimate (SE)	95% CI	<i>p</i>
Early-adulthood PA						
Total effect	0.072 (0.016)	[0.041, 0.103]	<.001	−0.021 (0.026)	[−0.072, 0.031]	.434
Direct effect						
Physical activity (early adulthood)	0.053 (0.020)	[0.015, 0.092]	.007	−0.060 (0.033)	[−0.125, 0.005]	.070
Specific indirect effects						
Physical activity (mid-adulthood)	0.017 (0.012)	[−0.006, 0.040]	.146	0.041 (0.020)	[0.002, 0.079]	.038
Hypertension	−0.001 (0.001)	[−0.003, 0.001]	.227	0.001 (0.001)	[−0.001, 0.003]	.284
Diabetes	0.000 (0.000)	[−0.001, 0.001]	.494	0.000 (0.001)	[−0.002, 0.001]	.537
Heart disease	−0.001 (0.001)	[−0.002, 0.001]	.289	0.000 (0.001)	[−0.002, 0.002]	.980
Physical activity (mid-adulthood), hypertension	0.003 (0.001)	[0.001, 0.005]	.004	−0.003 (0.002)	[−0.006, 0.000]	.073
Physical activity (mid-adulthood), diabetes	0.001 (0.001)	[0.000, 0.002]	.292	0.001 (0.001)	[−0.001, 0.003]	.396
Physical activity (mid-adulthood), heart disease	0.000 (0.000)	[0.000, 0.001]	.264	0.000 (0.001)	[−0.001, 0.001]	.980
Mid-adulthood PA						
Total effect	0.035 (0.019)	[−0.003, 0.073]	.071	0.064 (0.032)	[0.001, 0.128]	.048
Direct Effect						
Physical activity (mid-adulthood)	0.028 (0.019)	[−0.010, 0.066]	.145	0.067 (0.032)	[0.004, 0.131]	.038
Specific indirect effects						
Hypertension	0.005 (0.002)	[0.002, 0.008]	.004	−0.005 (0.003)	[−0.010, 0.000]	.073
Diabetes	0.001 (0.001)	[−0.001, 0.003]	.292	0.001 (0.002)	[−0.002, 0.004]	.396
Heart disease	0.001 (0.001)	[−0.001, 0.002]	.263	0.000 (0.001)	[−0.002, 0.002]	.980

Note: CI = confidence interval; PA = physical activity.

Predictive Value of Early Versus Mid-Adulthood PA

The positive associations of both early- and mid-adulthood PA with later-life episodic memory outcomes are in line with previous studies showing the benefits of adulthood PA and cardiorespiratory fitness on later-life cognitive health outcomes. Previous studies link greater PA or fitness in early- (8) or mid-adulthood (9–12) to lower dementia risk and better cognitive performance in older adulthood. In a female-only older adult sample, Middleton and colleagues (13) showed positive associations of both early- and mid-adulthood PA with later-life cognitive performance using a global dementia screening instrument at a single timepoint. Extending on these previous investigations, we utilized a measure of episodic memory, which has greater sensitivity for detecting age-related cognitive decline compared to global cognitive screening tests. Furthermore, because episodic memory was assessed up to 9 times over 16 years, the current study also extends previous cross-sectional findings (4) by showing independent and differential patterns of associations between adulthood PA and later-life initial memory level versus subsequent memory change. Together, these findings provide preliminary evidence that early- and mid-adulthood PA may add unique value to predictive models of late-life episodic memory and dementia risk, which could have important implications for the prevention of incident dementia.

PA Pathways Throughout Adulthood and Later-Life Memory

A key difference between Aim 1 and Aim 2 was that Aim 1 focused on the independent predictive value of early- versus mid-adulthood PA, so the association between these 2 exposures was modeled as a correlation (Figure 1). In contrast, Aim 2 focused on potential causal pathways involving PA during different adulthood periods as well as later-life cardiometabolic disease mechanisms and episodic memory. Because prior levels of PA may predict future PA levels, the relationship between early- and mid-adulthood PA was modeled as a regression path such that early-adulthood PA was a predictor of mid-adulthood PA (Figure 2). This aim allowed us to clarify whether early-adulthood PA might have a broader potential impact on late-life memory

through its association with mid-adulthood PA (ie, maintaining PA from early- to mid-adulthood). Indeed, results indicated that while the direct effect of early-adulthood PA (ie, the portion of the effect that was separate/unique from mid-adulthood PA) was limited to initial memory level, there were additional indirect effects of early-adulthood PA on both initial memory level and subsequent memory change via mid-adulthood PA. Notably, in the current study, a 1 *SD* increase in early-adulthood PA was equivalent to later-life memory level comparable to someone who is 3.3 years younger and a subsequent rate of memory change comparable to someone who is 0.5 years younger. Above and beyond PA in early adulthood, a 1 *SD* increase in mid-adulthood PA was equivalent to a subsequent rate of memory change comparable to someone who is 1 year younger. These findings suggest that both early- and mid-adulthood may represent critical periods for PA interventions to benefit later-life cognitive health and highlight the centrality of PA in early adulthood due to its broad effects on mid-adulthood PA as well as later-life cardiometabolic health, memory level, and subsequent memory change.

Previous studies show that PA levels typically decrease from early- to mid-adulthood, likely due to greater time demands from professional (eg, work-related stress) and personal (eg, family) responsibilities (32,33). While there were direct effects of early-adulthood PA on initial memory level in later-life independent of mid-adulthood PA, the only positive association between early-adulthood PA and later-life memory change was mediated by mid-adulthood PA. From a behavioral standpoint, healthcare professionals should encourage mid-adulthood PA, and intervention development efforts may consider strategies specifically targeted to facilitate initiating as well as maintaining mid-adulthood PA, in order to maximize its longitudinal cognitive benefits.

Cardiometabolic Pathways Linking Adulthood PA to Later-Life Memory

Another key difference between Aim 1 and Aim 2 was that Aim 2 examined potential cardiometabolic health pathways linking

adulthood PA to later-life memory trajectories. While substantial previous research has demonstrated that maintaining PA across adulthood is associated with better physical health in later-life, precise mechanisms underlying these associations remain unclear (5,15,16,34). In the current study, hypertension explained 4.2% of the effect of early-adulthood PA on initial memory level later in life, as well as 14.3% of the effect of mid-adulthood PA on initial memory level later in life. Thus, later-life hypertension appears to play a role in pathways from adulthood PA to later-life memory level. The association between greater mid-adulthood PA and reduced later-life hypertension is consistent with previous findings. Specifically, experimental research shows that PA confers benefits on cardiometabolic function broadly and on blood pressure regulation in particular (35). Results from the current study indicate that these positive effects of PA on blood pressure extend beyond concurrent associations. However, given that early-adulthood PA was only associated with later-life hypertension via mid-adulthood PA, maintaining PA over time appears critical, as the protective effects of PA on hypertension risk may eventually dissipate over longer time periods of inactivity. Better blood pressure control has been associated with better later-life cognitive function as well as lower risk for dementia (36). These associations may reflect the negative effects of hypertension on processes that regulate cerebral circulation, including endothelium-dependent processes, neurovascular coupling, and autoregulation, which contribute to structural and functional brain abnormalities (eg, white matter hyperintensities and reduced white matter integrity) that can underlie poor cognitive function (37–39).

Of note, in the current study, later-life hypertension was associated with concurrent memory level but not subsequent memory change. Findings from previous observational studies examining longitudinal associations between later-life hypertension and cognition are inconsistent. Several large-scale studies fail to show an association (40,41) while others document negative associations (42,43). Future investigations should consider the clinical complexity of hypertension (eg, duration of illness, medication adherence, daily blood pressure variability, and diastolic- versus systolic-specific effects) to clarify extant inconsistencies in hypertension-cognition associations.

In the current study, associations between adulthood PA and later-life memory were not mediated by later-life heart disease or diabetes. Similar to previous studies, more mid-adulthood PA was associated with a lower prevalence of later-life diabetes and heart disease (44); however, neither of these conditions was associated with memory level or change. Notably, there was a relatively low proportion of participants with diabetes (9.6%) or heart disease (11.5%) in this young older adult (61.16 ± 5.56) sample, compared to hypertension (39.2%), which may have limited our power to detect the effects of diabetes or heart disease on memory outcomes. Indeed, additional research using objective assessments of cardiometabolic disease is needed as the current study's self-report measures may underestimate the prevalence of these health conditions in the sample. For instance, prior findings in the HRS document associations between objective markers of diabetes (eg, hemoglobin A1c) and memory trajectories (45). Similarly, more fine-grained measures of heart disease that consider type (eg, myocardial infarction, peripheral vascular disease, chronic heart failure) and severity (eg, history of surgical intervention) may improve estimation of cardiometabolic disease effects on cognition.

Of note, the effects of early- and mid-adulthood PA on subsequent later-life memory decline were independent of cardiometabolic diseases. As described above, the use of objective cardiometabolic indicators may help clarify their potentially mediating role in the link between adulthood PA and later-life changes in memory. An

alternative interpretation is that cardiometabolic health may only underlie PA effects on other domains of cognitive function. Indeed, previous studies suggest negative effects of cardiometabolic diseases on declines in processing speed and executive functioning, but not memory (46), supporting a vasculopathic, rather than neurodegenerative, mechanism for cardiometabolic disease-related cognitive decline. However, contrasting findings from intervention studies suggest that PA confers beneficial effects on memory but not executive functioning in older adults with diabetes (47), highlighting the need for future longitudinal research to clarify vascular and neurodegenerative processes underlying cognitive decline and dementia. Furthermore, because previous research suggests that better cardiometabolic function may link mid-adulthood (17) and older adulthood (48) PA to later-life cognitive health outcomes, additional research is needed to clarify these discordant results. Notably, the HRS has not routinely measured processing speed and executive function cognitive domains, which limits the ability to examine longitudinal cognitive decline.

Even after accounting for the 3 indicators of cardiometabolic health, there were still significant associations between early-adulthood PA and initial memory level, as well as mid-adulthood PA and subsequent memory change. This pattern of results suggests that additional investigations of mechanisms linking lifecourse PA to later-life episodic memory are needed. Independent of its systemic effects, PA may confer future cognitive benefits via centrally mediated processes. Indeed, human and animal studies suggest that PA may confer resilience to brain aging and pathology by promoting inflammatory homeostasis (49) and hippocampal neurogenesis (50). For instance, intervention studies in humans have positively associated aerobic exercise with greater hippocampal volume, which contributed to better memory performance (50). PA may also confer beneficial cognitive effects via psychosocial pathways, as PA is associated with reductions in depressive symptoms, which in turn is associated with better cognitive function (51).

Limitations and Strengths

Although a preponderance of research has shown cognitive health benefits of PA, contrasting findings have been documented (52). The current study's limitations include the use of retrospective reports to measure early- and mid-adulthood PA. Of note, separate datasets using retrospectively reported PA show similar patterns of association with late-life mortality risk (22) and cognitive impairment (13). Previous studies also show adequate reliability of retrospectively and prospectively collected lifecourse psychosocial (53) and PA (54) data. Of note, retrospective reports of objective behaviors (eg, PA) may potentially be less prone to rating bias than subjective experiences (eg, affect or well-being) (55). Nevertheless, the current study's use of retrospectively reported PA necessitates caution when interpreting findings. Additional studies using prospectively collected, objective measures of PA are needed to improve estimates of the effects of lifecourse PA on later-life cognitive health.

Another limitation is that this study cannot rule out the possibility of reverse causation, as individuals with worse memory during adulthood may be less likely to exercise. One limitation of the HRS as well as many other longitudinal population-based survey studies of aging is that the clinical variables required to diagnose complex diseases such as mild cognitive impairment (MCI) and dementia are not collected. Therefore, it is not possible to statistically account for variance contributed and/or stratify analyses by these clinical groups. Notably, patterns of results persisted in sensitivity analyses that excluded older

adults with very low memory performance (-2 SD) at T1. Nevertheless, it is important to note that part of the memory decline described in the current study, as well as other studies in the HRS, may include participants transitioning into clinical states such as MCI and dementia. Another limitation of the current study is its use of a proxy measure of childhood SES. Although maternal education has been established as a proxy variable of childhood SES (29), future studies should incorporate a more robust measure. Of note, sensitivity analyses showed that observed associations persisted when maternal education was replaced with self-reported childhood family financial status.

Furthermore, the current study only used cardiometabolic disease data obtained at T1 in order to minimize reverse causation. Thus, it is possible that the observed findings underestimate the effects of early- and mid-adulthood PA on later-life cardiometabolic diseases and/or trajectories of memory functioning. Incorporating additional time points of cardiometabolic disease data in future studies may help clarify pathways via cardiometabolic diseases, particularly diabetes and heart disease which become more prevalent with advancing age.

Strengths of this study include examining 2 independent PA age periods in adulthood in order to test whether they represent critical periods for intervention. Another strength is the use of up to 16 years of episodic memory data in order to characterize PA associations with memory level versus change. The current study also featured a relatively large sample size and a comprehensive set of covariates, including an indicator of childhood SES. Furthermore, to minimize potential for reverse causation, we employed a time lag between the oldest possible age of PA reported (age 49) and youngest possible age of HRS study entry (age 55).

Conclusions

In summary, the current study suggests that both early- and mid-adulthood provide unique information in the prediction of later-life memory trajectories, and that both of these lifecourse periods may represent independent critical periods for engaging in PA in order to optimize late-life cognitive health. Adulthood PA may confer broad benefits that extend to later-life cardiometabolic and memory function, which highlights the critical importance of maintaining PA even with advancing age in order to obtain the entirety of its cardiometabolic and cognitive health benefits. Findings from these retrospective, observational data preclude a causal interpretation, and well-controlled studies are needed to test their replicability. Nevertheless, this study suggests that exercising in either early- or mid-adulthood, and maintaining PA across adulthood, may be uniquely protective for later-life cognitive health, and that hypertension may represent a key mediator of these effects.

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Conflict of Interest

None declared.

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Author Contributions

A.Z.K.: conception and design; analysis and interpretation of data; drafting of the article; and approval of final version; H.L.D.: interpretation of data, critical revisions, and approval of final version; N.S.: interpretation of data, critical revisions, and approval of final version; E.P.M.: interpretation of data, critical revisions, approval of and final version; K.S.: interpretation of data, critical revisions, and approval of final version; A.B.Z.: interpretation of data, critical revisions, and approval of final version; J.S.: interpretation of data, critical revisions, and approval of final version; L.B.Z.: conception and design; analysis and interpretation of data; critical revisions; and approval of final version.

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