HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Alzheimers Dement. 2019 February ; 15(2): 273–281. doi:10.1016/j.jalz.2018.08.008.

Leisure-Time Physical Activity Sustained Since Mid-life and Preservation of Cognitive Function: the Atherosclerosis Risk in Communities (ARIC) Study Cohort

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Abstract

Introduction: We tested the hypotheses that higher levels of and persistence of mid-life leisure-time physical activity (LTPA) are associated long-term with lower cognitive decline and less incident dementia.

Methods: 10,705 participants (mean age: 60 years) had LTPA (no, low, middle, or high) measured in 1987–1989 and 1993–1995. LTPA was assessed in relation to incident dementia and 14-year change in general cognitive performance.

Results: Over a median follow-up of 17.4 years, 1,063 dementia cases were observed. Compared with no LTPA, high LTPA in mid-life was associated with lower incident dementia (Hazard Ratio [95% CI], 0.71 [0.61, 0.86]) and lower declines in general cognitive performance (−0.07 standard deviation (SD) difference [−0.12, −0.04]). These associations were stronger when measured against persistence of midlife LTPA over 6 years.

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Disclosures

None

Discussion: LTPA is a readily modifiable factor associated inversely with long-term dementia incidence and cognitive decline.

Keywords

physical activity; cognitive decline; dementia

Introduction

Typical age-related cognitive decline occurs at 0.04–0.05 standard deviation (SD) units per year (0.5 SD/decade) in older adults.[1–3] This decline is greater among individuals with mild cognitive impairment[4] and can be accelerated by comorbidities.[5] Impaired cognition is associated with dependency in activities of daily living,[6] disability,[7] and healthcare costs.[8] Reducing the high burden of cognitive impairment and its sequelae in our rapidly aging population is a high priority that may be attainable by intervening on modifiable behaviors such as physical activity.

While participation in physical activity has been linked to improvements in muscular function, blood pressure, blood lipid levels, and lower risk of coronary heart disease,[9] physical activity may be dually beneficial for cognition. Mouse models indicate that exercise (e.g. treadmill running) improves cognition[10,11] and small clinical studies suggest that individuals who engage in aerobic exercise interventions have less cognitive decline than those who do not.[12] Randomized clinical trials (RCTs) have replicated this finding in humans for global cognition,[13,14] memory[15] and executive function,[15] but while the benefits from physical activity are expected to be most pronounced with sustained physical activity, most of the RCTs tested 6–12 month exercise interventions and only 50% of participants maintained the intervention level of physical activity for at least 3–6 months.[16,17] Several reports from epidemiologic studies of older adults are consistent with the RCTs.[18–21] Most studies were constrained by using assessments limited to global cognition.[18,19,21] Further, associations of physical activity with cognitive outcomes evaluated only in older adulthood, as in most published work, can be open to bias from reverse causality due to comorbidity and lifestyle changes associated with incipient cognitive impairment. Considering that dementia is a slowly progressive illness whose clinical manifestations may appear decades after pathophysiological changes in the brain have occurred,[22] too few studies to date have repeated measurements and length of follow-up sufficient to examine the role of physical activity from mid-life to older adulthood in its putative association with temporal decline in cognition and the risk of dementia.

Using data from the community-based Atherosclerosis Risk in Communities (ARIC) cohort study we sought to test the hypotheses that a single measure of physical activity in mid-life, and persistence of physical activity levels over 6 years in mid-life are associated with incident dementia and declines in cognitive function from mid- to late-life. As addressed here using repeated physical activity measurements and several domains of cognition over a prolonged follow-up, this study contributes to a limited body of observational studies that span several adult life epochs.

Methods

Study Population and Design

ARIC is a community-based prospective cohort study of atherosclerosis and cardiovascular disease. Enrollment began in 1987 with 15,792 participants aged 45–64 years recruited from 4 U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi). The baseline ARIC visit (1987–1989) was followed by three triennial visits (visit 2: 1990–1992, visit 3: 1993–1995, visit 4: 1996–1998), and a fifth visit occurring 15 years later in 2011–2013 (Figure 1). Detailed information about the ARIC Cohort has been described.[23] Based on the interest to examine levels of physical activity in mid-life and their persistence, our study baseline was defined as visit 3 (Figure 1). We excluded participants missing visit 3 information on leisure-time physical activity (n=2,933) or cognitive factor scores (n=2,045); those missing a physical activity assessment at ARIC visit 1 (n=4), and individuals with a dementia diagnosis prior to ARIC visit 3 (n=2). Due to small numbers, non-Black/non-White participants, and Blacks from Minneapolis and Washington County (n=103) were also excluded. Our initial analysis using the LTPA assessment at visit 3 as the exposure included 10,705 adults. The analysis of associations between persistent levels of LTPA in mid-life (visits 1 and 3) and cognitive outcomes excluded participants with inconsistent LTPA levels between the visits (n=6,072), yielding an analytic set of 4,633 participants (Supplemental Figure 1). Institutional review boards at each data collection site approved the study.

Exposure: Leisure-time Physical Activity (LTPA)

LTPA was measured at ARIC visits 1 (1987–1989) and 3 (1993–1995) using a standardized interviewer administered questionnaire[24], which asked, in open-ended form, about up to 4 leisure-time activities or sports played and the duration and frequency spent in each of the 4 leisure-time activities. Participants reported the number of hours within a week and number of weeks over a month that they performed each self-reported activity. Each activity was then assigned a metabolic-equivalent (MET) ranging from 1–12 METs based on the Compendium of Physical Activities.[25] For each activity reported, MET-minutes/week was estimated over the past year by multiplying the frequency, duration, and MET value.

LTPA, in MET-min/week, was also categorized: no LTPA (0 MET-min/week), followed by internally calculated tertiles of MET-min/week, at visits 1 and 3 separately, to assign low, middle or high LTPA. Persistent levels of LTPA in mid-life were identified among those who reported levels of activity grouped as no, low, middle, or high LTPA at both ARIC visits 1 and 3 (n=4,633).

Outcome: Incident Dementia

Using algorithms developed by the National Institute of Aging-Alzheimer's Association (NIA-AA) workgroups[26,27] and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5),[28] dementia diagnoses were determined among all participants that attended the ARIC Neurocognitive Study (NCS)/Visit 5 and completed the neuropsychological assessments.[29] An expert panel classified cognitive status based on results from neuropsychological test performance, functional assessments using the

subjective and informant-administered clinical dementia rating score (CDR) and functional assessment questionnaire (FAQ), neurological exam administered by trained staff, laboratory results, medications known to affect cognition, and neuropsychiatric symptoms assessed using the Neuropsychiatric Inventory. Two diagnostic reviewers (one physician and one neuropsychologist) assigned a diagnosis independently. Discordant cases were assigned to a third reviewer for adjudication. Additional dementia cases identified using a telephone instrument of cognitive status-modified (TICSm), informant interviews, hospitalization discharge codes and diagnostic codes from death certificates. Dementia cases identified from visit 3 (1993–1995) to the date of last participant contact up to September 1, 2013.

Outcome: Cognitive Function

Cognitive function was first measured at ARIC visit 2 (1990–1992) and again at visit 4 (1996–1998). A test of memory [delayed word recall], executive function/processing speed [Digit Symbol Substitution Test], and language [phonemic fluency] were administered. Cognitive function was assessed again at the ARIC-NCS/visit 5 (2011–2013) with a comprehensive neuropsychological battery. The following domains and cognitive tests were examined at visit 5: memory [delayed word recall, logical memory, and incidental learning], executive functioning/processing speed [Trail Making Tests, Parts A and B; Digit Symbol Substitution Test], and language [semantic and phonemic fluency, Boston Naming Test]. In order to maintain the temporal integrity of our study question, change in cognitive function was assessed from visits 4 to 5 only, after the last mid-life measurement of LTPA at visit 3 (Figure 1).

To account for differences in testing between visits 4 and 5, a factor score for general cognitive performance was derived using factor analysis as described previously[30] to identify common covariation between the cognitive tests in order to reduce measurement error when combining data across multiple cognitive tests. The interpretations of factor scores are similar to that for z scores because they were scaled to have a mean of 0 and variance of 1 at ARIC visit 2 (1990–1992) when the participant's cognitive function was first tested.

Covariates

Covariates include age, sociodemographic indicators (annual household income and neighborhood socioeconomic status summary score[31]); cigarette smoking status (never vs. ever); and apolipoprotein (APOE) ε4 genotype (0 or ≥ 1 allele). Neighborhood-level socioeconomic status was ascertained from census-tract level data. All covariates included in the regression models are drawn from ARIC visit 3, except race-field center (Minnesota Whites; Maryland Whites; North Carolina Whites; North Carolina Blacks; Mississippi Blacks), sex, and education (less than high school, high school or equivalent, and greater than high school), which were assessed at ARIC visit 1. Additional analyses adjusted for intermediate cardiovascular and lifestyle risk factors measured at ARIC visit 4 (1996–1998): diabetes mellitus (defined as fasting glucose ≥126 mg/dL or ≥ 200 mg/dL non-fasting glucose, self-reported history of physician-diagnosed diabetes, or use of diabetes mellitus medication); hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood

pressure ≥90 mmHg, or use of blood pressure-lowering medication); and body mass index (BMI, calculated as measured weight in kilograms divided by height in meters squared).

Statistical Analysis

Descriptive analysis used chi-square and ANOVA tests to examine differences in baseline (1993–1995) sociodemographic and disease characteristics across levels of mid-life LTPA (n=10,705) and persistent mid-life LTPA (n=4,633). Time to dementia was estimated using Cox proportional hazards regression models. For dementia cases ascertained since the ARIC-NCS/Visit 5 examination, dementia onset was defined as the date of ARIC-NCS/Visit 5 assessment. For other dementia cases, date of dementia onset was defined as the date of completion of the pertinent TICSm or informant interview, date of hospitalization discharge with a dementia ICD-9 code, or date of death certificate code with dementia, whichever came first. The potential lag between dementia onset and ascertainment of dementia using informant interviews, hospitalizations, or death was approximated by subtracting 6 months from these dates to assign a dementia date of onset. Participants without a dementia diagnosis were censored at the date of last participant contact up to September 1, 2013. We quantified the adjusted hazard for incident dementia across tertiles of low, middle, and high LTPA relative to no LTPA.

We examined the association between mid-life LTPA and persistence of mid-life LTPA with change in general cognitive performance factor score and domain-specific cognitive test z-scores from visit 4 (1996–1998) to visit 5 (2011–2013). Using time in study, we estimated mixed effects regressions with random intercepts and slopes to estimate the 14-year change (1996–2013) in cognition, specifying an independent covariance matrix for the random effects. Associations are estimated as differences in standard deviation units of decline.

Models were adjusted for age, education, race-ARIC field center, smoking status, APOE ε4, and individual- and neighborhood-level socioeconomic status. To assess the extent to which the association of LTPA with cognitive outcomes was influenced by vascular risk factor burden, additional analyses adjusted for visit 4 intermediate diabetes status, hypertension status, and BMI.

Attrition and selection biases are of concern in longitudinal data since healthier individuals, probably more physically active and cognitively intact, are more likely to stay in the study and bias the estimated associations toward the null. To address this, we conducted a sensitivity analysis incorporating multiple imputation by chained equation (MICE) methods[32] to account for bias in the analysis of cognitive change due to attrition. MICE utilizes extant information to account for individuals not observed in late-life. Variables included in the imputation models were determined based on *a priori* knowledge of their association with both cognitive function and the probability of dropout. Therefore, information used for the imputation of missing cognitive test scores included: TICSm, suspect dementia status, CDRs, prior cognitive z scores, and comorbid conditions assessed at annual telephone calls (e.g. coronary heart disease, diabetes status, hypertension status, history of stroke, self-reported health, and an indicator of whether a proxy report was needed). ARIC investigators previously validated the imputed scores.[33] All analyses were performed using STATA version 14.0 (StataCorp LLC, College Station, Texas).

Results

Baseline sociodemographic and clinical characteristics of the study population are presented in Table 1 by mid-life LTPA (n=10,705) and persistent mid-life LTPA (n=4,633). Less active participants were more likely to be Black, less educated, with a lower household income and neighborhood SES; and had a higher prevalence of diabetes and hypertension.

Leisure-time physical activity and incident dementia

Over a median follow-up of 17.4 years from 1993–2013, 1,063 participants developed dementia. Compared to participants who reported no LTPA in mid-life, having middle (hazard ratio (HR) = 0.77, 95% CI: 0.65–0.91) or high (HR=0.72, 95% CI: 0.61, 0.86) levels of LTPA was associated with lower rates of incident dementia (Table 2). Despite smaller numbers (n=475 dementia cases, Table 3), the HRs remained statistically significant among participants with persistently middle (HR= 0.65, 95% CI: 0.49, 0.87) or persistently high (HR= 0.75, 95% CI: 0.58, 0.97) LTPA in mid-life, compared to a persistent lack of LTPA in mid-life. The HR estimates were not substantially altered by further adjustment for intermediate diabetes, hypertension, and BMI (Tables 2 and 3).

Leisure-time physical activity and domain-specific change in cognitive function

The absolute, adjusted 14-year rate of change in general cognitive performance was estimated as −0.80 standard deviation (SD) (95% Confidence Interval (CI): −0.83, −0.77) in those not participating in LTPA in mid-life, and, estimated as −0.72 SD (95% CI: −0.75, −0.69) in those with high levels of LTPA in mid-life (Supplemental Table 1). Thus, compared to participants with high levels of LTPA in mid-life, not participating in LTPA was associated with a faster 14-year rate of decline in general cognitive performance (difference= −0.07 SD, 95% CI: −0.12, −0.04, Figure 2). Mid-life LTPA was not associated with changes in memory or language function (p >0.05); however, low levels of LTPA were associated with 0.05 SD less decline in executive function/processing speed compared to those with high levels of LTPA in mid-life.

Persistence of mid-life LTPA, measured over 6 years, conveyed stronger differences in 14-year rates of change in cognitive function. A persistent lack of LTPA in mid-life was associated with a steeper −0.10 SD difference (95% CI: −0.15, −0.05, Supplemental Table 2) in 14-year rate of decline in general cognitive performance, relative to participants with persistently high LTPA in mid-life. Persistently high LTPA in mid-life was also associated with greater declines in executive function/processing speed relative to persistently no or persistently low LTPA, but no significant difference in 14-year rates of change were observed in the domains of memory and language (p>0.05). All results were only slightly attenuated with further adjustment for intermediate diabetes, hypertension, and BMI.

Sensitivity Analyses

In sensitivity analyses incorporating MICE methods for cognitive change, inferences were not meaningfully changed by adjustment for bias due to attrition (data not shown). Consistent with this result, an examination of sociodemographic/clinical attributes across the

physically active and nonactive participants who were censored suggests that attrition bias would be minimal.

Discussion

In this population-based study, compared to high mid-life LTPA, we found that a lack of LTPA in mid-life is associated with greater rates of decline in cognitive function over 14 years and is associated with a higher incidence of dementia. The observed associations were strengthened among those with LTPA sustained through mid-life. The difference in 14-year rate of cognitive decline between those with a lack of persistent LTPA relative to those with persistently high LTPA in mid-life, equates to roughly a 12% greater cognitive decline from mid- to late-life. In comparison to other mid-life vascular risk factors examined in the ARIC study cohort, i.e. diabetes (19% greater decline[33]) and hypertension (6.5% greater decline[34]), not achieving high leisure-time physical activity in mid-life appears to be associated with a meaningful greater decline in cognitive function. The observed graded effects across the levels of LTPA indicate that higher LTPA was associated with less cognitive decline compared to low or middle LTPA.

Adjusting for intermediate vascular risk factors, including hypertension, diabetes, and BMI, slightly attenuated the results, suggesting that these factors may only partially mediate the effects of LTPA on cognitive change and incidence of dementia, supporting the view that there may be more direct paths between physical activity and cognitive outcomes. On the other hand, measurement error and temporal misalignment could have contributed to an incomplete assessment of mediation. Physical activity demonstrably influences structural changes in the brain through reorganization and neurogenesis,[35,36] likely in response to neurotrophic factors released by aerobic exercise.[37] Mouse models suggest that physical activity induces neurogenesis in the dentate gyrus of the hippocampus, resulting in increases in hippocampal volume[36] that are correlated with improved memory and executive function. A few clinical studies have found greater hippocampal volumes among more physically active older adults,[12,38] although this has not been widely studied in relation to physical activity at the population level.[12,38–40]

Findings to date on the role of physical activity on cognitive outcomes have been mixed, both from observational studies and short-term clinical trials.[41] Prior observational studies of physical activity and cognitive outcomes have been primarily cross-sectional in design or restricted to samples of older adults (≥ 65 years), while extant longitudinal studies [21,42] have generally been short (<10 years) and restricted to older adults. Although plausible, associations between physical activity and cognition in older adults with incomplete follow-up deserve careful scrutiny due to potential bias associated with ‘reverse causality’, comorbidity, and changes in lifestyle across adulthood. In an effort to address these issues, a recent prospective analysis by the Whitehall II Study of civil servants in London (aged 33–55 years) examined the role of time spent in mild, moderate to vigorous and total physical activity on 15-year change in cognitive function.[43] Contrary to our results, no association of physical activity with cognitive change or risk of dementia was observed. Discrepant findings may be due to the differences in age epochs in which changes in both physical activity and cognitive function were examined, as well as the low sensitivity of dementia

ascertainment in the Whitehall II cohort through linkage to electronic health records, particularly for milder cases of dementia, or to residual confounding. The few other longitudinal studies of mid-life physical activity have been limited to a single measurement of physical activity and have reported null associations with cognitive outcomes in late-life, in particular cognitive decline and risk of dementia.[44–46] Therefore, additional long-term population-based research is needed, as well as research to assess whether moderate levels of physical activity in population samples have detectable associations with cognitive function, whether physical activity is associated with structural changes in the brain, and whether specific patterns of physical activity relate to cognitive performance or the risk of clinically manifest dementia. Our results speak to some of these important questions in a community-based cohort followed for dementia for a median of 17.4 years.

Clinical trials of physical activity avoid the problem of reverse causation but the body of evidence from clinical trials is equivocal. Neither participation in an intensive lifestyle (diet and physical activity) intervention[47] nor a moderate-intensity physical activity intervention[48] improved cognitive function for high-risk sedentary middle-aged and older adults. Meta-analyses[49] that incorporate these and other clinical trial data concluded that physical activity does not protect against cognitive decline and dementia. The null findings from clinical trials may in part be due to the short duration of the interventions implemented, the age at which interventions were implemented, or possibly a suboptimal level of physical activity studied. Of relevance to cognitive health in populations, data are needed from observational studies on the effects of type, frequency, duration and intensity of physical activity on cognitive outcomes. Similarly, consideration of the association between physical activity and brain function across age/life epochs is needed to inform the design of future interventions aimed at preserving or improving cognitive outcomes.

There are limitations to this study. Only self-reported leisure-time physical activity was ascertained, which is known to overestimate more vigorous physical activity and underestimate sedentary time,[50] suggesting the need for studies that use both self-reported and objectively-measured physical activity. Attrition and selection biases are of concern when analyzing longitudinal data since those who drop out are more likely to be cognitively impaired, less healthy and less physically active, likely biasing associations towards the null. Our results were not substantially different in analyses that addressed potential bias due to attrition and death, however. Residual confounding remains a possibility as with all epidemiological studies, and PA and cognitive tests were not measured at the same visits. We also highlight the imprecision in the estimation of incidence dates for dementia; however, dementia adjudication was not available prior to the NCS exam.

Several strengths of our study can be noted, primarily its longitudinal design with long follow-up, the repeated measures of LTPA in mid-life, the use of objective measures of cognitive performance in three domains, and the adjudicated dementia outcomes. The consideration of mid-life LTPA and persistence of LTPA during mid-life contributes new knowledge on the role of physical activity on cognitive outcomes since our results are based on an unambiguous temporal sequence and reflect the leisure-time activities reported by the residents of four communities selected by criteria unrelated to the measurements of interest to this study. Furthermore, the long-term impact of mid-life leisure-time physical activity as

a modifiable element of lifestyle is of considerable interest in clinical settings and a public health perspective.

The incidence of dementia in an aging population lends urgency to the identification of modifiable risk factors, such as physical activity, that can be tested as targets of individual or population-wide interventions. The knowledge base on physical activity and brain health to date is constrained by several challenges, such as primarily insufficient follow-up time to assure the association is causal, mostly studies of older adults which may introduce reverse causality, but also the lack of validated exercise and comprehensive cognition measures, and the near impossibility of performing a long-term randomized controlled physical activity intervention. Testing a variety of physical activity prescriptions is needed to identify that which is most beneficial for brain health. No one prescription is likely to apply to our diverse populations, thus requiring population-based, observational studies of diverse, free-living individuals. In this population-level analysis of a community-based cohort, we observed a single measure of leisure-time physical activity and of physical activity sustained over a 6-year period to be associated with lower cognitive decline and lower incident dementia. Although this study highlights the potential benefit of higher levels of physical activity, we do not position to present any specific recommendation regarding the optimal dose, type, frequency, or duration of physical activity for brain health, and the data available to us do not permit such an analysis. Nonetheless, our findings contribute important information for future studies that can evaluate, in a diverse population, the joint and independent effects of type, frequency, duration, and intensity of physical activity on cognitive outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements/Conflicts/Funding Sources

The authors thank the staff and participants of the ARIC study for their important contributions. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). Neurocognitive data was collected by U01 HL096812, HL096814, HL096899, HL096902, and HL096917 with previous brain MRI examinations funded by R01-HL70825. Dr. Palta was supported by grant K99-AG052830 from the National Institute of Aging. Dr. Deal is supported by grant K01-AG054693 from the National Institute of Aging. Dr. Gross was supported by K01-AG050699 from the National Institute on Aging. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institute of Aging; the National Institutes of Health; or the U.S. Department of Health and Human Services.

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Research in Context

Systematic Review:

We reviewed the relevant literature using PubMed. Recent data suggests physical activity (PA) is associated with lower cognitive decline and less incident dementia. Additional population-based studies with repeated PA measurements and several domains of cognition over a prolonged follow-up are needed to sufficiently examine the role of PA from midlife to older adulthood and its putative association with temporal decline in cognition and the risk of dementia.

Interpretation:

Compared to high mid-life PA, we found that a lack of PA is associated with greater 14-year rates of decline in cognitive function and is associated with a higher dementia incidence.

Future Directions:

The long-term impact of mid-life leisure-time PA as a modifiable element of lifestyle is of considerable interest in clinical settings and from a public health perspective. Future studies are needed to evaluate the joint and independent effects of frequency, duration, and intensity of PA on cognitive outcomes.

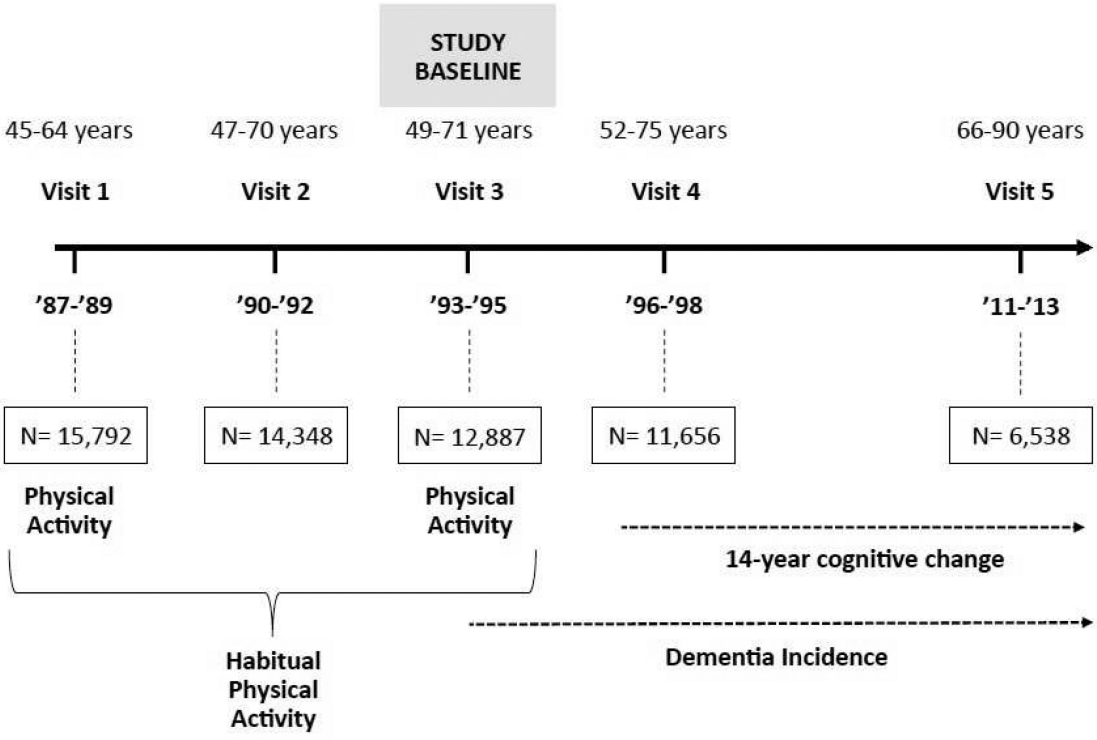

Fig. 1.
ARIC Study Timeline of Design and Measurements.

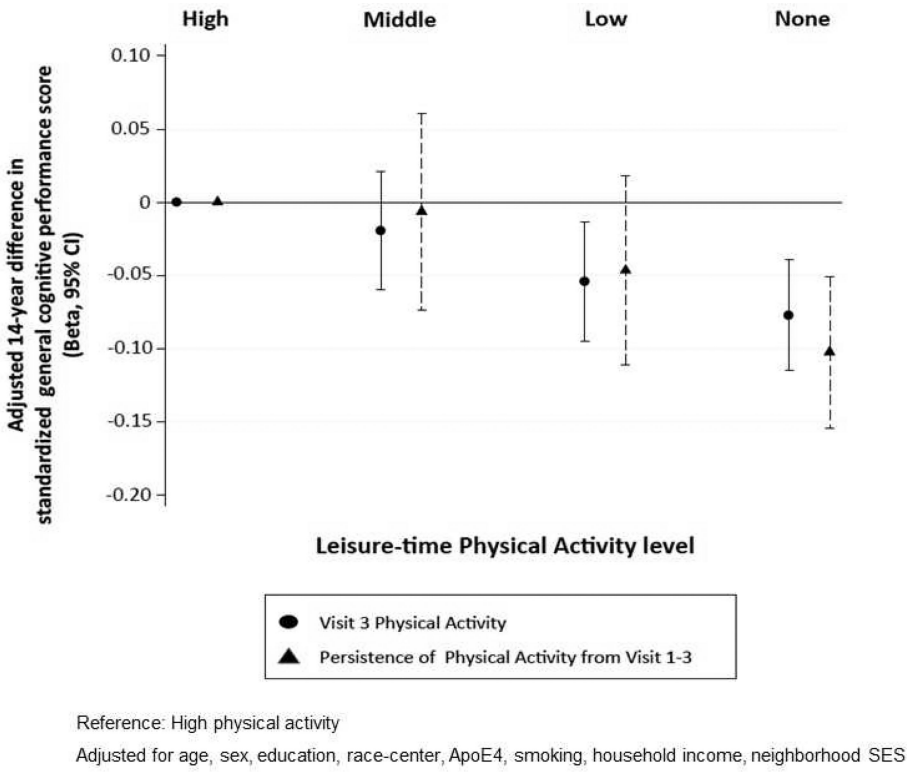

Fig. 2.

Adjusted 14-year difference (95% CI) in standardized general cognitive performance score, by midlife leisure-time physical activity (n = 10,705) and persistent midlife leisure-time physical activity (n = 4,633) levels, the ARIC cohort (1996–2013).

Table 1.

Participant characteristics at ARIC Visit 3 (1993–1995) across (1) leisure-time physical activity levels at ARIC visit 3 and (2) persistence of leisure-time physical activity levels from ARIC Visits 1–3

ARIC Visit 3 Participant Characteristics	Physical Activity ARIC Visit 3 n=10,705				Persistent Physical Activity ARIC Visits 1–3 n=4,633			
	No PA n=3590	Low n=2372	Middle n=2372	High n=2371	Persistently No PA n=1996	Persistently Low n=744	Persistently Middle n=699	Persistently High n=1194
MET-min/week (range)	0	1–608	609–1172	1173–7530	0	1–608	610–1171	1173–7530
Age, years, mean (SD)	59.4 (5.5)	59.7 (5.6)	60.5 (5.8)	60.3 (5.8)	59.1 (5.4)	59.4 (5.6)	60.6 (5.9)	60.2 (5.8)
Female sex, n (%)	2126 (59)	1527 (64)	1321 (56)	1015 (43)	1201 (60)	497 (67)	404 (58)	461 (39)
Black race, n (%)	945 (26)	447 (19)	380 (16)	303 (13)	673 (34)	142 (19)	85 (12)	95 (8)
< HS education, n (%)	920 (26)	378 (16)	341 (14)	238 (10)	581 (30)	100 (13)	75 (11)	78 (7)
Income ≥ $35,000, n (%)	1601 (45)	1225 (52)	1265 (53)	1495 (63)	831 (42)	415 (56)	388 (56)	847 (71)
NSES score, mean (SD)	−0.8 (5.1)	0.4 (5.0)	1.0 (5.0)	1.6 (5.0)	−1.4 (5.2)	0.6 (5.1)	1.4 (4.8)	2.6 (4.8)
Current smoker, n (%)	771 (22)	354 (15)	339 (14)	266 (11)	463 (23)	102 (14)	94 (13)	126 (11)
BMI, kg/m^2, mean (SD)	29.5 (6.1)	28.6 (5.4)	27.7 (4.9)	27.3 (4.5)	29.8 (6.3)	28.2 (5.4)	27.6 (5.0)	26.7 (4.1)
Current drinker, n (%)	1652 (46)	1262 (53)	1336 (56)	1548 (65)	872 (44)	404 (54)	416 (60)	850 (71)
Diabetes, n (%)	578 (16)	322 (14)	278 (12)	260 (11)	373 (19)	86 (12)	80 (12)	101 (9)
Hypertension, n (%)	1579 (44)	874 (37)	875 (37)	827 (35)	929 (47)	267 (36)	267 (38)	382 (32)

HS= High school

NSES= neighborhood socioeconomic status score

BMI= body mass index

Table 2.

Multivariable-adjusted Hazard Ratio (HR) estimates (95% CI) of incident dementia, by ARIC Visit 3 leisure-time physical activity levels (n=10,705), 1993–2013

Tertiles of MET-min/week at Visit 3	$N_{dementia}/N_{total}$	Model 1 n=10,705 HR (95% CI)	Model 2 n=10,613 HR (95% CI)
No PA	379/3590	Reference	Reference
Low	235/2372	0.88 (0.75, 1.04)	0.86 (0.73, 1.02)
Middle	233/2372	**0.77 (0.65, 0.91)***	**0.75 (0.63, 0.89)***
High	216/2371	**0.72 (0.61, 0.86)***	**0.71 (0.59, 0.85)***

* $p<0.05$

Model 1: Age, sex, education, race-center, APOE ε4, ever vs. never smoking status, annual household income, neighborhood SES summary score at Visit 3

Model 2: Model 1 + diabetes, hypertension, and body mass index at Visit 4

Alzheimers Dement. Author manuscript; available in PMC 2020 February 01.

Table 3.

Multivariable-adjusted Hazard Ratio estimates (95% CI) of incident dementia by persistence of leisure-time physical activity from visits 1–3 (n=4,633), 1993–2013

Persistence of Physical Activity from Visits 1–3	$N_{dementia}/N_{total}$	Model 1 n=4,633 Hazard Ratio (95% CI)	Model 2 n=4,590 Hazard Ratio (95% CI)
Pers. No PA	227/1996	Reference	Reference
Pers. Low	71/744	0.77 (0.58, 1.01)	**0.73 (0.55, 0.97)***
Pers. Middle	62/699	**0.65 (0.49, 0.87)***	**0.63 (0.47, 0.84)***
Pers. High	115/1194	**0.75 (0.58, 0.97)***	**0.71 (0.54, 0.92)***

*p<0.05

Model 1: Age, sex, education, race-center, APOE ε4, ever vs. never smoking status, annual household income, neighborhood SES summary score at Visit 3

Model 2: Model 1 + diabetes, hypertension, and body mass index at Visit 4