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Activity Energy Expenditure and Incident Cognitive Impairment in Older Adults

Laura E. Middleton, PhD; Todd M. Manini, PhD; Eleanor M. Simonsick, PhD; Tamara B. Harris, MD, MS; Deborah E. Barnes, PhD; Frances Tylavsky, DrPH; Jennifer S. Brach, PhD, PT; James E. Everhart, MD, MPH; Kristine Yaffe, MD

Background: Studies suggest that physically active people have reduced risk of incident cognitive impairment in late life. However, these studies are limited by reliance on self-reports of physical activity, which only moderately correlate with objective measures and often exclude activity not readily quantifiable by frequency and duration. The objective of this study was to investigate the relationship between activity energy expenditure (AEE), an objective measure of total activity, and incidence of cognitive impairment.

Methods: We calculated AEE as 90% of total energy expenditure (assessed during 2 weeks using doubly labeled water) minus resting metabolic rate (measured using indirect calorimetry) in 197 men and women (mean age, 74.8 years) who were free of mobility and cognitive impairments at study baseline (1998-1999). Cognitive function was assessed at baseline and 2 or 5 years later using the Modified Mini-Mental State Examination. Cognitive impairment was defined as a decline of at least 1.0 SD (9 points) between baseline and follow-up evaluations.

Results: After adjustment for baseline Modified Mini-Mental State Examination scores, demographics, fat-free mass, sleep duration, self-reported health, and diabetes mellitus, older adults in the highest sex-specific tertile of AEE had lower odds of incident cognitive impairment than those in the lowest tertile (odds ratio, 0.09; 95% confidence interval, 0.01-0.79). There was also a significant dose response between AEE and incidence of cognitive impairment ($P = .05$ for trend over tertiles).

Conclusions: These findings indicate that greater AEE may be protective against cognitive impairment in a dose-response manner. The significance of overall activity in contrast to vigorous or light activity should be determined.

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PHYSICAL ACTIVITY APPEARS TO be one of the more promising preventive strategies against cognitive impairment in the elderly population.[1] In most studies, people who are more physically active in midlife and late life have lower rates of dementia and cognitive impairment in late life.[2-5] In addition, people who participate in higher levels of physical activity have slower rates of cognitive decline compared with those who are less active.[6-8]

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A potential limitation of these studies is their reliance on self-reports of physical activity, which may include inaccurate reporting or misclassification, particularly in people with cognitive dysfunction. Although many physical activity questionnaires are considered valid and reliable measures of intentional physical activity, they have low to moderate correlation with objectively measured total daily physical activity.[9] Physical activity questionnaires usually focus on moderate or vigorous exercise-related physical activity, which is more readily quantifiable by frequency and duration, but do not adequately capture nonexercise, low-intensity physical activity, such as movement around the house, postural allocation, and fidgeting, which accounts for most activity energy expenditure (AEE) in people who do not regularly exercise.[10] Such activity may be important to health outcomes such as cognitive impairment. Indeed, a recent cross-sectional study[11] of older women identified a positive association between cognitive performance and total daytime movement as measured using actigraphy, which suggests that total activity may be important for cognitive outcomes.

Author Affiliations are listed at the end of this article.

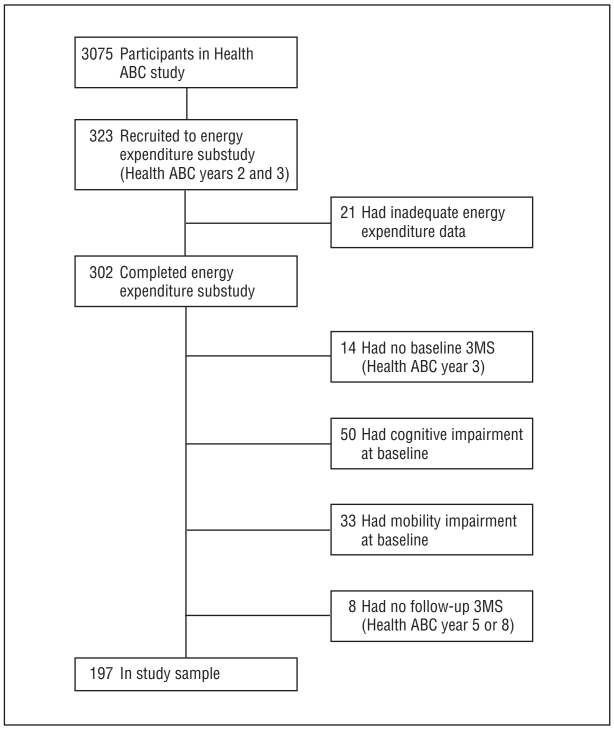

Figure. Selection of the study sample. Health ABC indicates Health, Aging, and Body Composition study; 3MS, Modified Mini-Mental State Examination.

Activity energy expenditure as measured by doubly labeled water (DLW) is considered to be the gold standard measure of total physical activity.[9] Activity energy expenditure captures energy expended on all physical activity, including moderate and vigorous physical activity (eg, jogging, walking, and biking) and low-intensity physical activity (eg, housework, daily chores, and postural allocation). People with higher levels of AEE have reduced rates of mortality and incident mobility impairment[12-14]; however, to our knowledge, no published prospective studies have examined the relationship between AEE and the incidence of cognitive impairment. Thus, this study aimed to examine the relationship between objectively assessed total physical activity as measured by AEE and incident cognitive impairment in late life.

METHODS

PARTICIPANTS

Participants were enrolled in the Health, Aging, and Body Composition (Health ABC) study, an ongoing prospective cohort study.[15] In brief, 3075 participants aged 70 to 79 years were recruited from a random sample of white Medicare beneficiaries and all age-eligible, self-identified black community residents at 2 centers (University of Pittsburgh, Pittsburgh, Pennsylvania, and University of Tennessee, Memphis) between 1997 and 1998. The participants included 51% women and 42% blacks. Participants were required to have no difficulty walking one-quarter of a mile (0.4 km), climbing 10 stairs, or performing basic activities of daily living at enrollment. In addition, they could have no plans to leave the area for the next 3 years and no evidence of life-threatening illnesses (eg, acute leukemia or melanoma). Written informed consent, as approved by the institutional review boards at each center, was obtained from each participant. The study was also approved by the study coordinating center (University of California, San Francisco) institutional review board.

People were randomly selected from the Health ABC cohort within sex and race strata and asked to participate in the energy expenditure substudy at year 2 or 3. The substudy enrolled 323 participants between 1998 and 1999, as previously described.[12,13] Of the 323 participants, 21 were excluded from the analyses because of failure to complete the protocol, lack of appropriate urine volume specimens, or failure of isotope or resting metabolic rate data to meet a priori quality control criteria (**Figure**). We also excluded those with no Modified Mini-Mental Examination (3MS) score at Health ABC year 3, which corresponds approximately to the energy expenditure substudy and served as the cognitive baseline (n=14). In addition, we excluded individuals with low cognitive performance at year 3 that may represent prevalent cognitive impairment (3MS score <80) (n=50) and those with mobility limitation (inability to walk 0.4 km) at the energy expenditure visit (an additional 33 participants), which may have impeded participation in physical activity and so would confound the analyses. Finally, we excluded participants with no follow-up 3MS score (n=8), to yield a final analytical sample of 197 (mean age, 74.8 years). Compared with the full Health ABC cohort, our study sample included a slightly greater proportion of blacks but otherwise was similar in age, sex, and self-reported physical activity (walking, stair climbing, working, volunteering, and caregiving).

DLW PROTOCOL

Total energy expenditure between 2 clinic visits was measured using DLW, as detailed elsewhere.[16] At the first visit, the participant ingested an estimated 2 g of DLW per kilogram of total body water and provided urine samples at approximately 2, 3, and 4 hours after the ingestion. At the second visit, approximately 15 days later, the participant provided 2 consecutive urine voids and a 5-mL blood sample was collected. The plasma was analyzed only if participants showed evidence of delayed isotopic equilibration (n=28).[16] Total energy expenditure was derived using the Weir[17] equation, as previously described.[12] Based on masked, repeat, urine isotopic analysis, the intratester repeatability of total energy expenditure was excellent (mean [SD] difference, 1.2% [5.4%], 16 participants) and compared well with that in a review article.[18]

RESTING METABOLIC RATE PROTOCOL

Resting metabolic rate was measured via indirect calorimetry using a respiratory gas analyzer (Deltatrac II; Datex Ohmeda, Inc, Helsinki, Finland), as detailed previously.[19] Testing occurred in the morning with the participant in a fasting state of at least 6 hours and after a 30-minute rest period after arrival at the center. A gas exchange hood was placed over the participant's head, and the metabolic rate was measured minute by minute for 40 minutes, with only the last 30 minutes used for calculation of the resting metabolic rate. Time periods that included participant movement or sleeping were also excluded from the resting metabolic rate calculation.

ACTIVITY ENERGY EXPENDITURE

Activity energy expenditure was calculated as 90% of total energy expenditure minus resting metabolic rate. The thermic effect of meals was estimated to account for the remaining 10% of total energy expenditure and was not included in the calculation of AEE.[20,21] Participants were classified into sex-specific tertiles of AEE for the purpose of these analyses.

SELF-REPORTED PHYSICAL ACTIVITY

At the first energy expenditure visit, an interviewer administered a questionnaire to ascertain physical activity over the previous 7 days. The questionnaire was a modified version of the Minnesota Leisure Time Activity Questionnaire,[22-24] which was adapted to include tasks applicable to older adults. The questionnaire captured the duration and intensity of walking for exercise, other walking, climbing stairs, working for pay, volunteering, and caregiving. This information was then converted to kilocalories per day based on intensity of activity.[25] Participants were divided into tertiles of self-reported physical activity based on reported kilocalories per week. Although participants were also asked whether they performed vigorous exercise, such as bicycling, swimming, jogging, racquet sports, stair stepping, rowing, or cross-country skiing, information on duration and intensity was not collected. Because only a few of our sample reported participation in vigorous exercise, we report the percentage of participation in vigorous exercise.

COGNITION

The 100-point 3MS was administered to participants at most Health ABC clinic visits. The 3MS is a brief test of global cognitive function with components for orientation, concentration, language, praxis, and immediate and delayed memory.[26] The 3MS score from year 3, which corresponds approximately to the energy expenditure substudy, was considered the baseline score for these analyses. Incident cognitive impairment was defined as a decline of at least 1.0 SD (9 points) from baseline to the most recent follow-up visit to Health ABC at year 5 or 8.[27]

OTHER MEASUREMENTS

At baseline, participants self-reported age, race, and years of education. At each visit, participants reported smoking history, hours per day sleeping or lying down, and level of difficulty walking 0.4 km. Participants' blood pressure, height, and weight were also measured at each visit. Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies–Depression Scale with a score of more than 15 indicative of high depressive symptoms.[28] Presence of medical conditions was determined from a combination of self-reported physician-diagnosed disease information, clinic data (eg, blood pressure), and medication use. Hypertension was diagnosed by self-report of a clinical diagnosis, use of an antihypertensive medication, and systolic blood pressure greater than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg at clinic visit. Diabetes mellitus was defined by self-report of a clinical diagnosis, use of diabetes drugs, fasting plasma glucose concentration higher than 126 mg/dL, or 2-hour post-challenge glucose concentration greater than 200 mg/dL. (To convert glucose level to millimoles per liter, multiply by 0.0555.) Apolipoprotein E (*APOE*) genotype was determined (Bioserve Biotechnologies, Ltd, Laurel, Maryland) and coded as *APOE* ε4 or no ε4. At the energy expenditure visit, fat-free mass was assessed using dual-energy x-ray absorptiometry (Hologic QDR 4500, software version 8.21; Hologic, Inc, Bedford, Massachusetts). Participants also reported their usual eating habits during the previous year. Estimated percentage of caloric intake from fat was derived from those reports.

STATISTICAL ANALYSIS

The participants' baseline characteristics were compared by sex-specific tertile of AEE and tertile of self-reported physical activity using analysis of variance for normally distributed continuous data, Kruskal-Wallis test for skewed continuous data, or χ^2 for categorical data. Follow-up *t* tests, Wilcoxon rank sum tests, or χ^2 test were conducted as necessary to differentiate between pairs of tertiles.

The correlation between AEE and self-reported physical activity (kilocalories per day) was examined using the Spearman rank correlation. Median and interquartile range of self-reported physical activity (overall and by type) were also described by sex-specific tertiles of AEE. Difference by sex-specific tertile was determined by Kruskal-Wallis equality-of-population rank test and follow-up Wilcoxon rank sum tests, as appropriate.

We conducted a series of logistic regressions to evaluate the odds of cognitive impairment during the follow-up period and trend for dose response by tertile of AEE and tertile of reported physical activity (models 1, 2, and 3). For all regression analyses, model 1 adjusted only for baseline 3MS score; model 2 adjusted for baseline 3MS score and demographics (age, educational level, sex, race, and site). Model 3 adjusted for baseline 3MS score, demographics, and variables that were associated with tertile of AEE or physical activity status ($P < .20$), as appropriate, in bivariable analyses. Trend across tertiles was determined by entering tertiles of AEE or self-reported physical activity into the logistic model as a continuous variable. Fit of models was determined using the Akaike information criterion. All statistical analyses were conducted using commercial software (SAS, version 9.1.3; SAS Institute, Inc, Cary, North Carolina).

RESULTS

There were some differences in participant characteristics across tertiles of AEE (**Table 1**). Participants who were in the middle and highest sex-specific tertiles of AEE were younger ($P < .001$ and $P = .02$, respectively) than those in the lowest tertile. People in the highest tertile of AEE were more frequently from the Pittsburgh site ($P = .01$). Those in the middle tertile of AEE slept less compared with people in the lowest tertile ($P = .006$). People did not vary significantly ($P > .05$) across tertile of AEE in race, education level, smoking, fat-free mass, percentage of dietary intake of fat, self-rated health, *APOE* ε4 allele, baseline 3MS score, and presence of diabetes, hypertension, or depression. Sex (lowest to highest tertile, female: 64.6%, 48.5%, and 37.9%; $P = .009$), race (black: 24.6%, 34.8%, and 47.0%; $P = .03$), fat-free mass (43.2 kg, 46.2 kg, and 50.7 kg; $P < .001$), sleep duration (8.4 hours, 8.8 hours, and 7.8 hours; $P = .02$), self-rated health (fair/poor: 13.8%, 18.2%, and 4.5%; $P = .05$), and diabetes mellitus (18.5%, 34.8%, and 39.4%; $P = .02$) were significantly different by tertile of self-reported physical activity. People did not vary significantly across tertile of self-reported physical activity in age, site, education level, smoking, percentage of dietary intake of fat, sleep, *APOE* ε4 allele, or depression.

Activity energy expenditure had a low but significant correlation with self-reported physical activity ($r = 0.19$, $P = .007$). Although self-reported physical activity was also significantly different across tertiles of AEE ($P < .001$,

Table 1. Baseline Characteristics of 197 Participants by Tertile of Daily Activity Energy Expenditure

Characteristic	Tertile of Activity Energy Expenditure, % (No.) Lowest (n = 65)	Middle (n = 66)	Highest (n = 66)	*P* Value[a]
Age, mean (SD), y	75.8 (3.0)	73.9 (2.9)	74.6 (2.9)	.002
Race, black	38 (25)	32 (21)	36 (24)	.72
Pittsburgh site	38 (25)	47 (31)	61 (40)	.04
Educational level, completed high school	83 (54)	88 (58)	80 (53)	.49
Ever smoker	51 (33)	616 (40)	61 (40)	.42
Fat-free mass, mean (SD), kg	45 (10.2)	47 (10.5)	48 (10.3)	.16
Dietary intake from fat, mean (SD), %	34 (7.5)	357 (7.5)	34 (7.9)	.86
Sleep, mean (SD), h/night	8.7 (2.1)	7.8 (1.6)	8.4 (2.4)	.03
Fair/poor self-rated health	18 (12)	11 (7)	8 (5)	.15
APOE ε4 allele[b]	35 (19/55)	36 (24/66)	32 (19/60)	.86
Depression	11 (7)	17 (11)	14 (9)	.62
Diabetes mellitus	32 (21)	38 (25)	23 (15)	.16
Hypertension	55.4 (36)	43.9 (29)	48.5 (32)	.42
Baseline 3MS score, mean (SD)	92.0 (5.1)	93.8 (4.6)	92.5 (5.0)	.10

Abbreviation: 3MS, Modified Mini-Mental State Examination.
[a] Significance was determined using analysis of variance or χ^2 tests for continuous and categorical variables, respectively.
[b] Only 55 participants, 66 participants, and 60 participants from the lowest, middle, and highest tertiles, respectively, had ApoE genotyping results.

Table 2. Self-reported Physical Activity in Relation to Tertile of AEE

Activity	Tertile of AEE, Median (IQR) Lowest (n = 65)	Middle (n = 66)	Highest (n = 66)	*P* Value
Total physical activity, kcal/d[a]	76.4 (24.4-196.9)	251.1 (66.0-578.5)	323.3 (112.4-596.5)	<.001
Exercise-related physical activity				
Participate in vigorous exercise, % (No.)[b,c]	21.5 (14)	22.7 (15)	18.2 (12)	.66
Walking for exercise, kcal/d	0 (0-38.8)	0 (0-46.7)	0 (0-69.6)	.55
Everyday physical activities, kcal/d				
Other walking	0 (0-0)	0 (0-0)	0 (0-30.4)	.07
Climbing stairs	1.3 (0-6.3)	5.9 (0.7-13.0)	6.3 (0.6-19.4)	.003
Paid work	0 (0-0)	0 (0-258.3)	0 (0-87.3)	.23
Volunteer work	0 (0-52.9)	20.5 (0-98.0)	2.8 (0-113.1)	.42
Caregiving	0 (0-0)	0 (0-0)	0 (0-49.1)	.03

Abbreviations: AEE, activity energy expenditure; IQR, interquartile range.
[a] Significance of difference was determined by Kruskal-Wallis equality-of-populations rank tests or a χ^2 test (high-intensity physical activity only).
[b] Because duration of vigorous exercise was not reported, it was not included in the calculation of total physical activity.
[c] Vigorous exercise includes participation in activities such as bicycling, swimming, jogging, racquet sports, stair stepping, rowing, or cross-country skiing.

Table 2), the difference between the middle and highest tertiles of AEE was not significant (median [interquartile range], 251.1 [66.0-578.5] kcal/d vs 323.3 [112.4-596.5] kcal/d; *P* = .54). Climbing stairs (*P* = .003) and caregiving (*P* = .03) were the only individual self-reported physical activities that were significantly different across tertiles of AEE (Table 2).

Tertile of AEE was strongly associated with the likelihood of incident cognitive impairment. The incidence of cognitive impairment during the follow-up period was 1.5% in the highest tertile of AEE, followed by 4.5% in the middle tertile and 16.9% in the lowest tertile. In analyses adjusted only for baseline 3MS score (model 1: Akaike information criterion, 125.0), participants in the middle and highest tertiles of AEE were less likely to have incident cognitive impairment during the 5-year follow-up period than were those in the lowest tertile (middle tertile: odds ratio [OR], 0.23; 95% confidence interval [CI], 0.06-0.88; and highest tertile: OR, 0.07; 95% CI, 0.01-0.60) (**Table 3**). When demographics were included in the model (model 2: Akaike information criterion, 125.6) (Table 1), those in the highest tertile had a lower rate of cognitive impairment than those in the lowest tertile (OR, 0.09; 95% CI, 0.01-0.74). Although the difference between those in the middle and lowest tertiles was no longer statistically significant, there was a dose response across tertiles, and participants with higher AEE had lower rates of incident cognitive impairment (*P* = .03 for trend). Even after controlling for additional factors that were associated with tertile of AEE (fat-free mass, sleep duration, self-rated health, and diabetes) (model 3: Akaike information criterion, 107.8), the odds of cognitive impairment remained significantly lower among participants in the highest tertile of AEE than among those

Table 3. Incidence and Odds of Significant Cognitive Decline[a] During the Follow-up Period by Tertile of AEE and Self-reported Physical Activity

Tertile	Odds Ratio (95% Confidence Interval)[b]		
	Model 1	Model 2	Model 3
AEE			
Lowest	1 [Reference]	1 [Reference]	1 [Reference]
Middle	0.23 (0.06-0.88)	0.30 (0.07-1.23)	0.28 (0.06-1.23)
Highest	0.07 (0.01-0.60)	0.09 (0.01-0.74)	0.09 (0.01-0.79)
P value for trend	.01	.03	.05
Self-reported physical activity			
Lowest	1 [Reference]	1 [Reference]	1 [Reference]
Middle	0.29 (0.07-1.13)	0.35 (0.08-1.57)	0.40 (0.08-1.95)
Highest	0.29 (0.07-1.13)	0.23 (0.05-1.05)	0.31 (0.06-1.55)
P value for trend	.05	.05	.13

Abbreviations: AEE, activity energy expenditure; 3MS, Modified Mini-Mental State Examination.
[a] Cognitive decline indicated as change of at least 1.0 SD (9 points) on the 3MS.
[b] Model 1 was adjusted for baseline 3MS; model 2, for baseline 3MS, demographics (age, sex, race, site, and years of education); and model 3, AEE was adjusted for baseline 3MS, demographics, fat-free mass, sleep duration, self-rated health, and diabetes mellitus, and physical activity was adjusted for baseline 3MS, demographics, smoking history, fat-free mass, sleep duration, self-rated health, and diabetes.

in the lowest (OR, 0.09; 95% CI, 0.01-0.79). In contrast, there was no significant difference in the likelihood of incident cognitive impairment across tertile of self-reported physical activity in any of the models (Table 3), and the dose response was significant in models 1 and 2 (*P*=.05 for each) but not in model 3 (*P*=.13).

COMMENT

In this study, older adults with higher objectively measured total daily activity had a lower incidence of cognitive impairment. The association between cognitive impairment and AEE was stronger and more dose-dependent than for self-reported physical activity. However, the relative contribution of total physical activity, moderate or vigorous physical activity, and low-intensity physical activity is unclear.

Despite many previous studies[2-7,29] suggesting that people who are more physically active have lower risk of cognitive impairment in old age, there remains concern that the results of these studies may be biased because of the use of self-reported physical activity. The results of this study allay these concerns by using an objective and all-encompassing measure of activity (AEE) to confirm that activity is inversely associated with the likelihood of developing incident cognitive impairment. Indeed, in this study, AEE had a strong dose-response relationship with the rates of incident cognitive impairment. The difference in the odds of incident cognitive impairment between the highest and lowest tertiles of AEE reported herein is more disparate than reported in most,[4] but not all,[30] previous studies of self-reported physical activity.

From the present study, the effect of total physical activity vs that of moderate or vigorous physical activity or light activity is unclear. However, it is possible that the more significant, dose-dependent association between cognitive impairment and AEE vs self-reported physical activity was the result of more accurate capture of low-intensity physical activity, such as movement around the house, postural allocation, and fidgeting. Questionnaires to quantify low-intensity, nonexercise physical activity, which is not easily quantified in frequencies and durations, have not been developed.[31,32] Future studies should examine the role of very low-intensity physical activity in optimizing cognitive outcomes in late life.

Future studies also should consider using AEE in combination with self-reports and accelerometry to decipher any differences in the association between moderate or vigorous physical activity, activity of daily living, and very low-intensity physical activity and the maintenance of cognition in old age. It may be particularly important to capture low-intensity physical activity in elderly individuals, who are less likely to perform vigorous physical activity.[33] In this sample, AEE was more strongly associated with caregiving and stair climbing, 2 activities of daily living, than with participation in vigorous exercise or exercise-related walking.

Despite growing evidence to support an association between greater physical activity and better cognition, it remains possible that low activity is a premorbid indicator of vulnerability to cognitive impairment rather than a determinant of cognitive health. Indeed, frailty, which is a risk factor for incident cognitive impairment,[34,35] is defined by loss of strength and weight loss, which would contribute to low AEE. To minimize the likelihood that AEE is simply a symptom of poor cognition or health, we eliminated people with mobility impairment or very low cognitive performance (3MS score <80) at our study's baseline and controlled for numerous health indicators associated with AEE. However, measurement of total activity might be an effective means to identify people at risk for cognitive decline early in its course regardless of whether low total activity is a determinant of cognitive health or merely an indicator of vulnerability.

The mechanisms by which physical activity is related to late-life cognition are likely to be multifactorial. Research[36-38] suggests that physical activity may improve neuroplasticity by modifying levels of brain-derived neurotrophic factor. Physical activity is also associated with reduced accumulation of β-amyloid plaque—one of the hallmark features of Alzheimer disease—in animal models.[39] Finally, physical activity is associated with reduced rates and severity of vascular risk factors, including hypertension, obesity, and type 2 diabetes mellitus,[40] each of which is associated with increased risk of cognitive impairment.[41-43] However, it is unclear how low-intensity physical activity is related to each of these mechanisms; this is another topic that needs attention in future studies.

Our study has several strengths. Most important, we used an accurate, encompassing, objective measure of physical activity to examine the relationship between total physical activity and cognitive impairment. In addition, our participants were well characterized, so we were able to control for many possible confounders, including age, educational level, baseline cognition, and comorbidities. However, the study also has some limitations. Because of the expense of DLW methods, our study sample was small, providing us with limited power to detect associations of cognitive impairment with self-reported physical activity. Furthermore, the energy expenditure substudy was not powered to detect differences in cognitive outcomes. In addition, although our sample was similar to the full Health ABC cohort in age, sex, mobility, walking ability, and physical activity, there may be undetermined differences. In this study, cognitive impairment was defined by a decline of at least 1.0 SD (9 points) on the 3MS rather than by a comprehensive clinical diagnosis, which may cause misclassification. However, as little as a 5-point decline in the 3MS score is clinically meaningful.[44] Self-reported physical activity reflected only the previous week vs 2 weeks for AEE and thus may be less likely to reflect normal physical activity levels and the relationship to cognitive impairment. Finally, we did not account for seasonal variation in AEE; however, this is more likely to weaken rather than strengthen the relationship between AEE and cognitive impairment.

Our study provides new evidence that objectively measured total daily activity, as measured by energy expenditure, is associated with a reduced incidence of cognitive impairment in older adults. The contribution of moderate and vigorous physical activity vs low-intensity physical activity to this relationship remains unclear; future longitudinal studies should examine the role of moderate and vigorous physical activity vs low-intensity physical activity in maintaining cognitive independence for older adults. We are optimistic that even low-intensity activity of daily living may be protective against incident cognitive impairment.

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Author Affiliations: Heart and Stroke Foundation Centre for Stroke Recovery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Dr Middleton); Department of Aging and Geriatric Research, University of Florida, Gainesville (Dr Manini); Clinical Research Branch (Dr Simonsick) and Laboratory of Epidemiology, Demography, and Biometry (Dr Harris), National Institute on Aging, Bethesda, Maryland; Department of Psychiatry, San Francisco Veterans Affairs Medical Center, San Francisco, California (Drs Barnes and Yaffe); Departments of Psychiatry (Drs Barnes and Yaffe), Neurology (Dr Yaffe), and Epidemiology and Biostatistics (Dr Yaffe), School of Medicine, University of California, San Francisco; Department of Biostatistics and Epidemiology, University of Tennessee, Memphis (Dr Tylavsky); Department of Physical Therapy, University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Brach); and Epidemiology and Data Systems Program, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (Dr Everhart).
Correspondence: Laura E. Middleton, PhD, Heart and Stroke Foundation Centre for Stroke Recovery, Sunnybrook Research Institute, 2075 Bayview Ave, A421, Toronto, ON M4N 3M5, Canada (Middleton_l@hotmail.com).
Author Contributions: Dr Middleton had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Manini, Tylavsky, and Everhart. *Acquisition of data:* Simonsick and Harris. *Analysis and interpretation of data:* Middleton, Manini, Barnes, Brach, and Yaffe. *Drafting of the manuscript:* Middleton, Manini, and Tylavsky. *Critical revision of the manuscript for important intellectual content:* Middleton, Manini, Harris, Barnes, Brach, Everhart, and Yaffe. *Statistical analysis:* Middleton and Manini. *Obtained funding:* Harris, Tylavsky, and Everhart. *Administrative, technical, and material support:* Simomsick, Harris, and Yaffe. *Study supervision:* Yaffe.
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