



## Physical Activity, *APOE* Genotype, and Dementia Risk: Findings from the Cardiovascular Health Cognition Study

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Physical activity may help preserve cognitive function and decrease dementia risk, but epidemiologic findings are inconsistent. The authors conducted a prospective study to determine the association between physical activity and risk of dementia, Alzheimer's disease, and vascular dementia. The US study population comprised 3,375 men and women aged 65 years or older, free of dementia at baseline, who participated in the Cardiovascular Health Cognition Study in 1992–2000. Leisure-time energy expenditure and an activity index reflecting number of different physical activities were calculated. Analyses were based on Cox proportional hazards models. There were 480 incident cases of dementia over an average of 5.4 years of follow-up. After multivariate adjustment, participants in the highest quartile of physical energy expenditure had a relative risk of dementia of 0.85 (95% confidence interval: 0.61, 1.19) compared with those in the lowest quartile, and participants engaging in  $\geq 4$  activities had a relative risk of dementia of 0.51 (95% confidence interval: 0.33, 0.79) compared with those engaging in 0–1 activity. These associations were more marked in apolipoprotein E genotype (*APOE*)  $\epsilon 4$  allele noncarriers but were absent in carriers. A similar pattern was observed for Alzheimer's disease and vascular dementia. Mechanisms to explain the observed relations deserve further study.

aged; Alzheimer disease; dementia; exercise; motor activity; physical fitness; risk factors

Abbreviations: *APOE*, apolipoprotein E genotype; CHCS, Cardiovascular Health Cognition Study; CHS, Cardiovascular Health Study; MRI, magnetic resonance imaging; 3MS, Modified Mini-Mental State.

Dementia, a condition characterized by a global decline in cognitive functioning, is a major public health problem worldwide. An estimated 1.9–4 million persons are currently living with Alzheimer's disease, the most common type of dementia, in the United States alone (1). Unless an effective preventive strategy is realized, the number of dementia cases is expected to expand as the number of persons living into

later decades continues to increase (2). Advancing age, family history of dementia, educational level, and presence of the apolipoprotein E genotype (*APOE*)  $\epsilon 4$  allele remain the only established risk factors for Alzheimer's disease (3).

A mounting body of evidence supports the role of physical activity as a means to maintain cognitive performance. Physical activity may preserve neuronal plasticity, increase

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synapses and dendritic receptors following injury, and release hormonal factors that may assist in neuronal creation and function (brain-derived neurotrophic factor, epinephrine) (4). In addition, physical activity lowers cardiovascular risk, decreases blood pressure, and increases high density lipoprotein cholesterol levels and glucose tolerance (5), each of which may be related to neuronal integrity and cognitive function (6, 7). Finally, engaging in physical activity may indicate a more enriched social environment, which may decrease dementia risk (8).

Several randomized trials have reported enhanced neurocognitive function following exercise training (9). In addition, observational studies (10–13) have shown an inverse association between physical activity and cognitive decline among older adults. However, an inverse association between physical activity and Alzheimer's disease has been found in some (10, 14–19), but not all (20–23), studies. Diminished physical activity may also have different roles in the various forms of dementia.

In this study, we examined the relation of physical activity to incident dementia and its subtypes, Alzheimer's disease and vascular dementia, by using data from a large, community-based cohort of older adults. We also assessed the possibility that the association of physical activity with dementia may be different for *APOE*  $\epsilon 4$  carriers versus noncarriers.

## MATERIALS AND METHODS

### Subject selection

The Cardiovascular Health Study (CHS) is a population-based, prospective cohort study initiated in 1989 to identify factors related to cardiovascular disease in older adults (24). The target population consisted of adults aged 65 years or older residing in one of four US communities: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh, Pennsylvania. Eligible persons were drawn from the Health Care Financing Administration Medicare enrollment lists by random sampling in each of three age strata (65–74, 75–84, and  $\geq 85$  years). A total of 5,201 men and women agreed to participate in the initial recruiting phase in 1989–1991. An additional 687 African Americans joined the study in 1992–1993 (total  $N = 5,888$ ).

The Cardiovascular Health Cognition Study (CHCS) (25–27), an ancillary study of the CHS, was started in 1992 when all CHS participants were invited to undergo cerebral magnetic resonance imaging (MRI) and to participate in cognitive testing. The CHCS cohort consisted of 3,660 (66.8 percent participation rate (28)) persons for whom brain MRIs were available; 3,608 of these persons had both MRI and measures of cognition assessed at this time. Compared with nonparticipants, CHCS participants were younger, more educated, and less likely to have cardiovascular disease (29). The institutional review boards at each participating institution approved the research protocols for both the CHS and CHCS. All participants provided written informed consent.

### Data collection

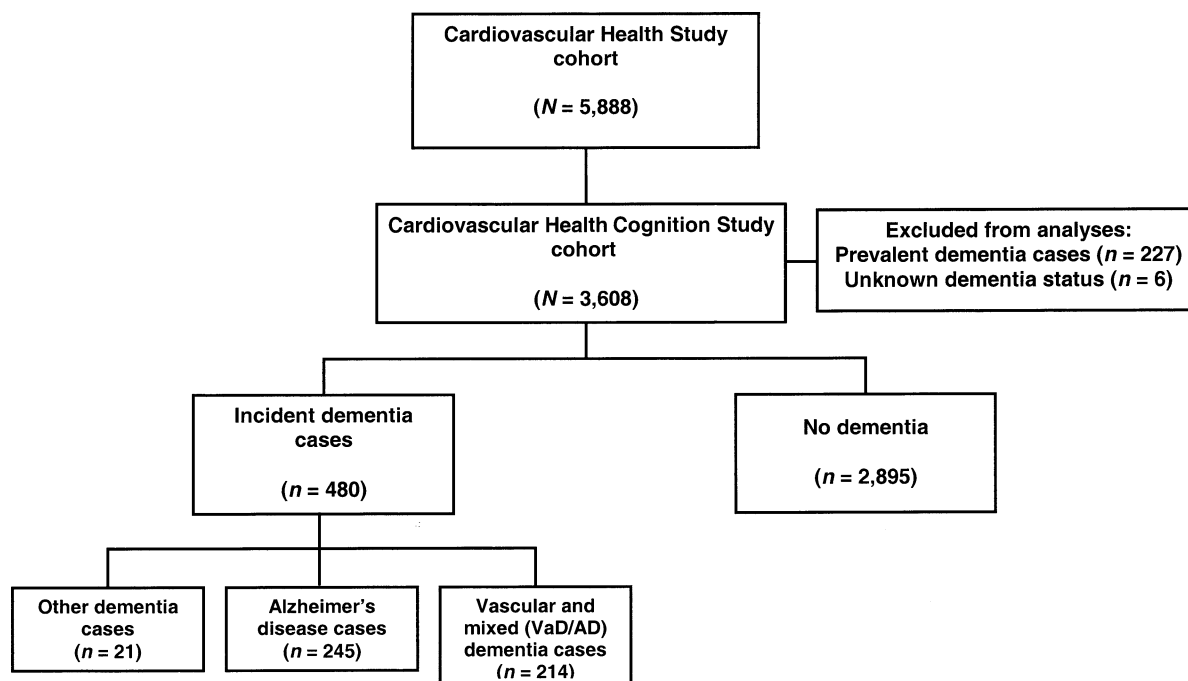
**Physical activity.** Information on physical activity was collected by trained interviewers at CHS baseline (1989–1990) and at CHCS baseline (1992–1994). A modified Minnesota Leisure Time Activity Questionnaire (30, 31) asked participants about the frequency and duration of 15 different types of activities over the previous 2 weeks. These activities were selected because they were previously shown to be the most common among older adults (32). Included were walking, household chores, mowing, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golfing, general exercise, and swimming.

Activities were assigned metabolic equivalents (ml O<sub>2</sub>/minute: METs) according to intensity (30), and leisure-time energy expenditure (kilocalories/week) was estimated for each person. Kilocalorie expenditure at CHS baseline and CHCS baseline were averaged to obtain an estimate of habitual physical activity levels in older adulthood used for the current analysis. Only a single measure of physical activity was used for participants for whom values were missing at one of the testing periods ( $n = 416$ ).

To express the diversity of physical activity, an activity index was calculated as the number of different activities each subject participated in over the previous 2 weeks. Raking and mowing were collapsed into a single category to represent “yard work,” resulting in a potential range for the index of 0–14 activities. The activity indices from CHS baseline and CHCS baseline were averaged to represent the activity index used in the present study. Similar aggregate scores for physical activity have been used in previous studies of dementia risk (16–19).

***APOE* genotyping.** Methods for *APOE* genotyping in CHS have been described elsewhere (29). Briefly, genomic DNA was extracted from whole-blood samples and was amplified by using polymerase chain reaction. After cleaving and electrophoresis on agarose gels, restriction patterns were determined according to the methods of Hixson and Vernier (33). *APOE* genotypes were grouped as *APOE*  $\epsilon 4$  carriers ( $\epsilon 2/\epsilon 4$ ,  $\epsilon 3/\epsilon 4$ ,  $\epsilon 4/\epsilon 4$  genotypes) and noncarriers ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 2/\epsilon 3$ ,  $\epsilon 3/\epsilon 3$  genotypes).

**Other covariates.** Other measurements obtained during the CHCS baseline examination were also considered. Sociodemographic variables included age, gender, educational level, and ethnicity. Information on smoking, alcohol intake, and postmenopausal hormone replacement therapy use was self-reported. Prevalent cases of myocardial infarction, angina, stroke, transient ischemic attack, and congestive heart failure at baseline were ascertained by participant self-report of a physician's diagnosis. Functional impairment was measured by using a modified version of the instrument for assessing basic activities of daily living and instrumental activities of daily living from the National Health Interview Survey (34). Social network was assessed by using the Lubben Social Network Scale (35), and a series of questions asking participants about life satisfaction and personal relationships was summed to represent a measure of social support. The Center for Epidemiologic Studies Depression Scale (36) was administered at CHCS baseline, and a more sensitive version of the Mini-Mental State Examination, the



**FIGURE 1.** Cardiovascular Health Cognition Study sample selection (1992–1993) and follow-up (1999–2000), United States. VaD, vascular dementia; AD, Alzheimer's disease.

Modified Mini-Mental State (3MS) Examination (37), was administered annually. The 3MS assesses several domains of cognition in greater detail than the Mini-Mental State Examination does, with scores ranging from 0 to 100; higher scores reflect better performance. If a person did not receive a clinical evaluation, attempts were made to evaluate cognition by using the Telephone Interview for Cognitive Status (38). For participants who died between examinations, further information was obtained by using the Informant Questionnaire for Cognitive Decline in the Elderly (39) and data concerning circumstances of death.

Self-reported weight and height were also recorded at CHCS baseline. Body mass index was calculated as weight (kilograms) per height (meters) squared. Blood pressure was measured in a standardized manner by trained personnel after the participant had been seated for 5 minutes. The average of two readings was calculated for analysis. Hypertension was defined as a previous diagnosis of hypertension, taking hypertensive medication, or having a current systolic blood pressure of  $\geq 140$  mmHg or a diastolic blood pressure of  $\geq 90$  mmHg. Total cholesterol, high density lipoprotein cholesterol, and triglycerides were determined in fasting samples by using standard methods, and low density lipoprotein cholesterol was estimated by the Friedewald formula (40). Persons were considered diabetic if they had a validated medical diagnosis of diabetes or a fasting glucose level of 126 mg/dl or higher.

Cerebral MRIs conducted at CHCS baseline were scored for overall severity of white-matter lesions according to the scale developed by CHS researchers (41). A white-matter-lesion severity score of  $< 3$  was considered within normal

limits for this group of older adults, whereas a score of  $\geq 3$  was considered indicative of neurodegenerative changes.

#### Diagnosis of dementia

Dementia status and type in CHCS were classified in 1999–2000 by using a multistage process (25–27). Initially, participants were classified at their local study site into a dementia risk stratum (high or low). Persons were deemed high risk if they 1) had a 3MS score of  $< 80$  within the last two study visits, 2) had a decline of  $\geq 5$  points on the 3MS within their follow-up period, 3) had a Telephone Interview for Cognitive Status score of  $< 28$  or an Informant Questionnaire for Cognitive Decline in the Elderly score of  $> 3.6$ , 4) had an incident stroke, 5) had a diagnosis of dementia that was documented in medical records, or 6) resided in a nursing home during the study period.

At the Pittsburgh site, all participants who were alive and could be traced were invited to the center in 1999–2000 for a full neuropsychiatric examination, regardless of dementia risk. At the three remaining sites, high-risk participants (as described above), all minority participants, and participants for whom cognitive data were incomplete were invited for a comprehensive evaluation. For those who did not attend the clinic visit, medical records and proxy or previous telephone interviews were used for diagnosis. The diagnosis was based on a deficit in performance in two or more cognitive domains sufficiently severe to affect the subjects' activities of daily living for those with a history of normal intellectual function. The dementia criteria were designed to identify

**TABLE 1. Baseline characteristics\* of participants in the Cardiovascular Health Cognition Study, United States, 1992–2000**

Variable	Overall (N = 3,375)	Noncases (n = 2,895)	Incident dementia cases (n = 480)	p value†
Age (years)	74.8 (4.9)	74.3 (4.6)	78.0 (5.5)	<0.0001
Gender: female	59.1	59.0	59.6	0.81
Race: Caucasian	85.0	85.2	83.5	0.35
Education (no. of years)	12.7 (3.0)	12.8 (2.9)	12.2 (3.2)	0.0001
Body mass index (weight (kg)/height (m) <sup>2</sup> )	26.7 (4.5)	26.8 (4.5)	26.1 (4.6)	<0.001
3MS‡ Examination score	92.2 (6.3)	92.9 (5.9)	88.2 (7.1)	<0.0001
APOE§ ε4	24.1	22.6	34.0	<0.001
Comorbid condition				
Stroke or transient ischemic attack	6.6	5.7	11.5	<0.001
Myocardial infarction or angina	19.7	18.9	24.6	<0.01
Congestive heart failure	4.6	4.4	5.4	0.33
Diabetes	25.1	24.9	26.5	0.46
Hypertension	57.4	56.4	62.9	<0.01
≥1 ADL‡ difficulty	9.7	8.9	14.4	<0.001
≥1 IADL‡ difficulty	22.9	21.7	30.2	<0.001
Depression score	4.9 (4.7)	4.8 (4.6)	5.8 (5.1)	<0.0001
Energy expenditure (kcal/week)	1,212.6 (1,388.4)	1,236.0 (1,407.1)	1,071.3 (1,261.7)	0.02
No. of activities during the previous 2 weeks	2.6 (0.02)	2.6 (0.02)	2.3 (0.05)	<0.0001
Alcohol intake ≥1 drink/week	35.4	37.3	25.0	<0.001
Current smoker	9.3	9.3	8.8	0.18
Estrogen replacement therapy user¶	13.9	14.8	8.4	<0.01
High density lipoprotein cholesterol (mg/dl)	53.8 (14.6)	53.8 (14.7)	53.5 (14.0)	0.80
Low density lipoprotein cholesterol (mg/dl)	127.3 (33.5)	127.3 (33.5)	127.7 (34.0)	0.64
Triglycerides (mg/dl)	141.8 (79.4)	141.9 (79.2)	141.7 (80.4)	0.97
Carotid maximum intima-media thickness (mm)	1.41 (0.55)	1.38 (0.53)	1.58 (0.65)	<0.0001
Magnetic resonance imaging white-matter grade ≥3	33.3	30.0	53.2	<0.001

\* Values are expressed as mean (standard deviation) or as %.

†  $\chi^2$  or *t* test comparing incident dementia cases with noncases.

‡ 3MS, Modified Mini-Mental State; ADL, activities of daily living; IADL, instrumental activities of daily living.

§ Apolipoprotein E genotype (APOE) was available for only 3,075 participants (412 cases, 2,663 noncases).

¶ For 1,994 female participants only (286 cases, 1,708 noncases).

subjects with syndromes that could include relatively preserved memory functions (e.g., frontotemporal dementia), and thus memory deficit was not required for the diagnosis of dementia (26).

All participants identified as having dementia were reviewed by the Adjudication Committee, made up of neurology and psychiatry experts. The diagnosis of Alzheimer's disease was based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (42) criteria, and the diagnosis of vascular dementia was based on Alzheimer's Disease Diagnostic and Treatment Centers criteria (43). Time of dementia onset was established by the first diagnosis if recorded in medical records and otherwise as the midpoint between two annual CHS follow-up interviews with a marked change in cognition leading to the final dementia diagnosis.

## Statistical analyses

Survival analysis was used to assess the association between activity level and time to onset of dementia by using Cox proportional hazards regression. Multivariate models were adjusted for age, gender, race, APOE genotype, educational level, difficulty in activities of daily living and instrumental activities of daily living, Lubben Social Network Scale, social support, baseline 3MS score, and white-matter grade. Hazard ratios and 95 percent confidence intervals were computed. Tests for linear trend across quartiles of physical activity were computed by introducing into the Cox models a variable with the median of each quartile as a continuous variable. Effect modification was assessed by stratification and by introducing product terms in multivariate Cox models. All statistical analyses were performed by using Stata software, version 7.0 (44).

**TABLE 2. Participant characteristics\* by quartile of leisure-time energy expenditure, Cardiovascular Health Cognition Study, United States, 1992–2000**

Variable	Quartile 1: <248 kcal/week (n = 844)	Quartile 2: 248–742 kcal/week (n = 842)	Quartile 3: 743–1,657 kcal/week (n = 844)	Quartile 4: >1,657 kcal/week (n = 843)	p value†
Age (years)	75.2 (5.1)	74.9 (5.1)	74.7 (4.9)	74.4 (4.4)	<0.01
Gender: female	75.7	68.3	55.7	36.8	<0.001
Race: Caucasian	73.6	86.5	87.9	91.9	<0.001
Education (no. of years)	12.1 (3.1)	12.6 (3.0)	12.9 (2.9)	13.2 (2.8)	<0.001
Body mass index (weight (kg)/height (m) <sup>2</sup> )	27.6 (5.3)	26.7 (4.4)	26.4 (4.1)	26.2 (3.9)	<0.001
3MS‡ Examination score	91.1 (6.9)	92.3 (5.9)	92.6 (6.4)	93.0 (5.6)	<0.001
APOE‡ ε4	21.0	23.0	26.1	26.2	0.02
Comorbid condition					
Stroke or transient ischemic attack	6.8	7.2	6.6	5.6	0.20
Myocardial infarction or angina	21.6	18.2	18.3	20.6	0.85
Congestive heart failure	6.5	3.6	4.6	3.4	0.03
Diabetes	29.5	23.2	25.4	22.4	<0.01
Hypertension	63.4	57.4	53.3	55.4	<0.01
≥1 ADL‡ difficulty	17.4	9.0	6.6	5.7	<0.001
≥1 IADL‡ difficulty	34.7	22.8	21.1	12.9	<0.001
Depression score	5.9 (5.0)	5.4 (4.9)	4.5 (4.4)	4.1 (4.0)	<0.001
No. of activities during the previous 2 weeks	1.5 (0.6)	2.4 (0.8)	3.0 (0.9)	3.5 (0.8)	<0.001
Alcohol intake ≥1 drink/week	25.0	31.8	37.7	47.7	<0.001
Current smoker	11.1	9.9	8.2	7.8	0.02
Estrogen replacement therapy user	11.1	15.3	13.6	17.4	0.02
High density lipoprotein cholesterol (mg/dl)	54.2 (14.5)	54.6 (14.7)	53.8 (14.7)	52.6 (14.5)	<0.01
Low density lipoprotein cholesterol (mg/dl)	128.2 (34.3)	126.6 (32.5)	127.9 (35.4)	126.7 (31.9)	0.55
Triglycerides (mg/dl)	149.6 (89.3)	146.3 (83.7)	137.2 (69.1)	134.4 (73.1)	<0.001
Carotid maximum intima-media thickness (mm)	1.4 (0.55)	1.4 (0.55)	1.4 (0.56)	1.4 (0.55)	0.67
Magnetic resonance imaging white-matter grade ≥3	36.2	35.6	31.4	30.0	<0.01
Follow-up time (no. of years)	5.2 (1.7)	5.4 (1.8)	5.5 (1.6)	5.6 (1.6)	<0.001

\* Values are expressed as mean (standard deviation) or as %.

† Test for trend across quartiles of leisure-time energy expenditure.

‡ 3MS, Modified Mini-Mental State; APOE, apolipoprotein E genotype; ADL, activities of daily living; IADL, instrumental activities of daily living.

## RESULTS

Of the 3,608 CHCS participants, we excluded 227 who had dementia at baseline and six whose dementia status could not be determined. Of the remaining 3,375 subjects, 480 developed incident dementia over 5.4 years of follow-up (median, 6.0; range, 0.03–8.4 years) (figure 1).

Table 1 describes participant characteristics at CHCS baseline. Those who developed dementia, when compared with those who did not, were older, had a lower educational

level, were more likely to carry the APOE ε4 allele, had poorer cognitive performance on the 3MS at baseline, had more physical difficulties, and were more likely to show white-matter disease on cerebral MRI. Incident dementia cases were also more likely to have a history of stroke or cardiovascular disease and to have hypertension.

On average, leisure-time physical activity expenditure was 1,213 kcal per week (standard deviation, 1,388), but 304 participants were completely sedentary (leisure-time kilocalorie expenditure = 0). Most persons reported

**TABLE 3. Participant characteristics\* by activity index (no. of activities during the previous 2 weeks), Cardiovascular Health Cognition Study, United States, 1992–2000**

Variable	0–1 activity (n = 674)	2 activities (n = 946)	3 activities (n = 861)	≥4 activities (n = 892)	p value†
Age (years)	76.1 (5.2)	75.0 (5.1)	74.4 (4.7)	74.0 (4.3)	<0.001
Gender: female	69.4	65.2	58.9	45.1	<0.001
Race: Caucasian	74.0	84.7	87.7	90.9	<0.001
Education (no. of years)	12.2 (3.1)	12.3 (3.0)	12.9 (2.9)	13.3 (2.7)	<0.001
Body mass index (weight (kg)/height (m) <sup>2</sup> )	27.4 (5.2)	26.7 (4.6)	26.8 (4.3)	26.1 (3.9)	<0.001
3MS‡ Examination score	90.8 (6.9)	91.7 (6.5)	92.9 (5.8)	93.3 (5.6)	<0.001
APOE§ ε4	20.1	25.4	24.4	25.3	0.065
Comorbid condition					
Stroke or transient ischemic attack	9.1	5.9	5.6	6.3	0.053
Myocardial infarction or angina	24.8	19.9	18.0	17.2	<0.001
Congestive heart failure	6.8	4.9	3.6	3.4	<0.01
Diabetes	31.9	25.7	21.4	23.0	<0.001
Hypertension	62.2	59.0	55.4	53.9	<0.001
≥1 ADL‡ difficulty	18.6	11.0	5.8	5.4	<0.001
≥1 IADL‡ difficulty	39.3	27.6	15.6	12.6	<0.001
Depression score	6.1 (5.4)	5.2 (4.7)	4.6 (4.4)	4.1 (4.0)	<0.001
Alcohol intake ≥1 drink/week	24.1	31.1	36.8	47.8	<0.001
Current smoker	11.4	9.3	9.2	7.6	0.39
Estrogen replacement therapy user	9.8	13.1	14.0	19.7	<0.001
High density lipoprotein cholesterol (mg/dl)	53.5 (14.6)	54.2 (14.4)	54.1 (14.3)	53.2 (15.1)	0.524
Low density lipoprotein cholesterol (mg/dl)	127.2 (35.0)	125.6 (32.9)	128.8 (33.7)	127.9 (32.8)	0.267
Triglycerides (mg/dl)	150.5 (92.1)	141.9 (74.7)	139.9 (79.5)	137.2 (73.3)	0.002
Carotid maximum intima-media thickness (mm)	1.5 (0.58)	1.4 (0.54)	1.4 (0.55)	1.4 (0.54)	0.082
Magnetic resonance imaging white-matter grade ≥3	40.9	34.3	31.9	27.9	<0.001
Follow-up time (no. of years)	4.9 (1.9)	5.4 (1.8)	5.5 (1.6)	5.7 (1.5)	<0.001

\* Values are expressed as mean (standard deviation) or as %.

† Test for trend across quartiles of activity index.

‡ 3MS, Modified Mini-Mental State; ADL, activities of daily living; IADL, instrumental activities of daily living.

§ Apolipoprotein E genotype (APOE) was available for only 3,073 participants (612 in quartile 1; 861 in quartile 2; 783 in quartile 3; 817 in quartile 4).

engaging in 2–3 different activities (mean, 2.7; standard deviation, 1.4). Walking and household chores were the most common, with 77.5 percent and 83.0 percent of active persons engaging in these activities, respectively. Approximately one third of the sample engaged in each of the activities of gardening, yard work, or an organized exercise program.

The relation between physical activity and other participant characteristics is displayed in table 2. For males, Caucasians, participants with higher educational levels, and persons with fewer functional difficulties (activities of daily living/instrumental activities of daily living), levels of physical activity were higher. Relatively sedentary participants (quartile 1) were more likely to be hypertensive, to be diabetic, to smoke, and to have higher levels of high density lipoprotein cholesterol and triglycerides compared with more active participants. Similar associations were found between

baseline characteristics and the activity index for number of activities (table 3). The Spearman correlation between energy expenditure and the activity index was 0.69 ( $p < 0.001$ ).

Leisure-time energy expenditure was inversely associated with the risk of dementia, although, after adjustment for age and other covariates, the trend was no longer significant (table 4). The point estimates suggested an inverse relation for Alzheimer's disease and vascular dementia, but none of the analyses for vascular dementia reached significance.

Number of physical activities was inversely associated with dementia risk (table 5). This inverse association persisted after multivariate adjustment. Adjusted hazard ratios for all-cause dementia incidence were 1.0 (reference), 0.90, 0.90, and 0.58 for 0–1, 2, 3, and 4 or more activities, respectively ( $p$ -trend = 0.004). The trend remained significant in models that further adjusted for total energy expenditure (data not shown).

**TABLE 4. Hazard ratios of incident dementia by level of leisure-time energy expenditure, Cardiovascular Health Cognition Study, United States, 1992–2000\***

	<248 kcal/week	248–742 kcal/week	743–1,657 kcal/week	>1,657 kcal/week	<i>p</i> -trend
<b>All-cause dementia</b>					
No. of incident cases	129	136	111	103	
Incidence rate (per 1,000 PY†)	29.5	30.2	23.9	21.8	
Crude HR† (95% CI†)	1.0 (referent)	1.03 (0.81, 1.31)	0.81 (0.63, 1.05)	0.74 (0.57, 0.96)	<0.01
Age-adjusted HR (95% CI)	1.0 (referent)	1.05 (0.65, 1.33)	0.84 (0.65, 1.08)	0.82 (0.64, 1.07)	0.07
Multivariate‡ HR (95% CI)	1.0 (referent)	1.22 (0.93, 1.60)	0.94 (0.69, 1.28)	0.85 (0.61, 1.19)	0.11
<b>Alzheimer's disease</b>					
No. of incident cases	69	70	58	48	
Incidence rate (per 1,000 PY)	15.8	15.5	12.5	10.2	
Crude HR (95% CI)	1.0 (referent)	0.99 (0.71, 1.38)	0.79 (0.56, 1.12)	0.64 (0.45, 0.93)	<0.01
Age-adjusted HR (95% CI)	1.0 (referent)	1.0 (0.72, 1.40)	0.81 (0.57, 1.15)	0.71 (0.49, 1.03)	0.04
Multivariate‡ HR (95% CI)	1.0 (referent)	1.07 (0.73, 1.57)	0.92 (0.62, 1.39)	0.70 (0.44, 1.13)	0.08
<b>Vascular dementia</b>					
No. of incident cases	55	58	52	48	
Incidence rate (per 1,000 PY)	12.6	12.9	11.2	10.2	
Crude HR (95% CI)	1.0 (referent)	1.04 (0.72, 1.50)	0.90 (0.62, 1.31)	0.82 (0.56, 1.21)	0.23
Age-adjusted HR (95% CI)	1.0 (referent)	1.05 (0.73, 1.52)	0.93 (0.63, 1.35)	0.92 (0.62, 1.35)	0.54
Multivariate‡ HR (95% CI)	1.0 (referent)	1.32 (0.89, 1.96)	0.99 (0.63, 1.57)	1.03 (0.64, 1.67)	0.70

\* No. of participants in crude and age-adjusted models = 3,373; *n* = 3,041 for fully adjusted models.

† PY, person-years; HR, hazard ratio; CI, confidence interval.

‡ The multivariate model was adjusted for age (continuous), educational level (continuous), gender, ethnicity (Caucasian or non-Caucasian), apolipoprotein E genotype (*APOE* (ε4 or non-ε4), baseline Modified Mini-Mental State Examination score (continuous), magnetic resonance imaging white-matter-grade score (<3 or ≥3), activities of daily living impairment (<1 or ≥1), instrumental activities of daily living impairment (<1 or ≥1), Lubben Social Network Score (continuous), and social support score (continuous).

When analyses were stratified by *APOE* ε4 carrier state, the inverse association of energy expenditure and activity index with dementia risk was limited to *APOE* ε4 non-carriers (table 6 and figure 2). The multivariate-adjusted hazard ratios for all-type dementia comparing the highest with the lowest quartile of energy expenditure in *APOE* ε4 noncarriers was 0.68 (*p*-trend = 0.01), and the hazard ratio comparing the highest with the lowest quartile of activity index was 0.44 (*p*-trend < 0.001). The corresponding hazard ratios for energy expenditure and activity index for *APOE* ε4 carriers were 1.29 (*p*-trend = 0.53) and 1.20 (*p*-trend = 0.68). The *p* values for the interaction of energy expenditure or activity index with *APOE* ε4 carrier status were 0.06 and 0.003, respectively. The same pattern was observed for Alzheimer's disease and vascular dementia (figure 2).

Persons may be less active because they are less physically able to be active. Therefore, we repeated the analysis by excluding subjects with one or more instrumental activities of daily living impairments and with one or more activities of daily living impairments, but the associations of energy expenditure and the activity index with dementia risk and the effect modification with *APOE* carrier status were similar.

## DISCUSSION

In this large, prospective cohort study of community-dwelling older adults, we identified an inverse association between physical activity and dementia risk for *APOE* ε4 noncarriers but found no association for *APOE* ε4 carriers. The associations were similar for Alzheimer's disease and vascular dementia. Our results also suggest that participating in a number of different activities may be as or more important than frequency, intensity, and duration of physical activity with respect to dementia risk.

Findings from prospective studies of physical activity and dementia have been inconsistent (10, 15–17, 19, 22, 23, 45). Among Japanese elders, regular physical activity was associated with lower risk of Alzheimer's disease but not with vascular dementia incidence (15). Similarly, older French participants who engaged in three or more social or leisure activities, versus none, had an 80 percent lower overall dementia risk (16, 17). In the Canadian Study of Health and Aging, physical activity was inversely associated with all-cause dementia and Alzheimer's disease (10), but an inverse association with vascular dementia was observed for women only (45). Wang et al. (22), however, did not

**TABLE 5. Hazard ratios of incident dementia by activity index (no. of activities during the previous 2 weeks), Cardiovascular Health Cognition Study, United States, 1992–2000\***

	0–1 activity	2 activities	3 activities	≥4 activities	p-trend
<b>All-cause dementia</b>					
No. of incident cases	130	152	113	84	
Incidence rate (per 1,000 PY†)	39.5	29.8	23.7	16.5	
Crude HR† (95% CI†)	1.0 (referent)	0.76 (0.60, 0.96)	0.60 (0.47, 0.78)	0.42 (0.32, 0.55)	<0.001
Age-adjusted HR (95% CI)	1.0 (referent)	0.88 (0.69, 1.11)	0.76 (0.59, 0.97)	0.55 (0.42, 0.73)	<0.001
Multivariate‡ HR (95% CI)	1.0 (referent)	0.90 (0.69, 1.18)	0.90 (0.66, 1.22)	0.58 (0.41, 0.83)	0.004
<b>Alzheimer's disease</b>					
No. of incident cases	69	72	61	43	
Incidence rate (per 1,000 PY)	21.0	14.1	12.8	8.4	
Crude HR (95% CI)	1.0 (referent)	0.68 (0.48, 0.94)	0.61 (0.43, 0.86)	0.40 (0.27, 0.58)	<0.001
Age-adjusted HR (95% CI)	1.0 (referent)	0.78 (0.56, 1.09)	0.76 (0.54, 1.08)	0.52 (0.36, 0.77)	0.001
Multivariate‡ HR (95% CI)	1.0 (referent)	0.73 (0.49, 1.08)	0.85 (0.57, 1.29)	0.55 (0.34, 0.88)	0.03
<b>Vascular dementia</b>					
No. of incident cases	55	71	50	37	
Incidence rate (per 1,000 PY)	16.7	13.9	10.5	7.3	
Crude HR (95% CI)	1.0 (referent)	0.85 (0.60, 1.20)	0.64 (0.43, 0.94)	0.44 (0.29, 0.67)	<0.001
Age-adjusted HR (95% CI)	1.0 (referent)	0.98 (0.69, 1.39)	0.81 (0.55, 1.19)	0.59 (0.39, 0.90)	0.01
Multivariate‡ HR (95% CI)	1.0 (referent)	1.09 (0.74, 1.60)	1.01 (0.64, 1.58)	0.65 (0.39, 1.08)	0.08

\* No. of participants in crude and age-adjusted models = 3,373;  $n = 3,041$  for fully adjusted models.

† PY, person-years; HR, hazard ratio; CI, confidence interval.

‡ The multivariate model was adjusted for age (continuous), educational level (continuous), gender, ethnicity (Caucasian or non-Caucasian), apolipoprotein E genotype (*APOE*) ( $\epsilon 4$  or non- $\epsilon 4$ ), baseline Modified Mini-Mental State Examination score (continuous), magnetic resonance imaging white-matter-grade score ( $<3$  or  $\geq 3$ ), activities of daily living impairment ( $<1$  or  $\geq 1$ ), instrumental activities of daily living impairment ( $<1$  or  $\geq 1$ ), Lubben Social Network Score (continuous), and social support score (continuous).

observe an association of physical activity with dementia incidence once social, mental, and productive activities were accounted for, although these investigators examined only three types of physical activities and few subjects participated in these activities. The Religious Orders Study (23) and the Bronx Aging Study (21) also failed to identify a relation between activities that were physical per se and the risk of dementia but did report an association between cognitive activity and reduced dementia incidence. Neither of these studies accounted for *APOE* genotype in the analysis, however. Although we did not measure cognitive activities directly, physical activities often occur in conjunction with social and cognitive stimulation.

Physical activity may protect against dementia risk through several mechanisms. Experimental studies have demonstrated that physical exercise activity facilitates learning, increasing the expression of genes promoting neurogenesis and neural plasticity (4, 46). Although several neural substrates may mediate exercise-induced effects on neuronal structure and integrity, research suggests a central role of brain-derived neurotrophic factor (4, 46), and levels of this factor in the hippocampi are diminished in patients with Alzheimer's disease (47). Nonneural vascular adaptations are also enhanced with exercise, including increased cerebral blood flow and substrate exchange (48), increased

cerebral capillary density (49), and decreased accumulation of radical oxidative proteins (50).

In addition, physical activity may be a surrogate for overall "life engagement" and greater social activity. Persons with more developed social networks have a lower risk of all-cause mortality than persons who are socially isolated, and social supports attenuate the rate of cognitive decline in older adults (51). Social networks may also promote overall health, particularly cardiovascular risk factors, and thereby may impact dementia risk. Similarly, involvement in physical activities is associated with mastery and self-efficacy (52). In turn, these attributes may motivate persons to be more attentive to health needs and health behaviors. We adjusted for social network and social support in multivariate models, however, and the activity index continued to be associated with dementia risk. If physical activity is operating through social mechanisms, it appears to be at a level not captured by these two measures of social functioning.

Involvement in a number of different activities likely requires the organization and memory skills necessary to flexibly schedule, attend, and shift among activities. Both organizational, or executive, and memory processes are regulated by neuroanatomical regions adversely affected by aging and dementing illnesses. Exercising may help buffer



**TABLE 6. Hazard ratios of incident dementia by level of physical activity, stratified by APOE,\* Cardiovascular Health Cognition Study, United States, 1992–2000†**

	Leisure-time energy expenditure				<i>p</i> -trend
	<248 kcal/week	248–742 kcal/week	743–1,657 kcal/week	>1,657 kcal/week	
<i>All-cause dementia</i>					
<i>APOE</i> ε4 noncarriers					
No. of incident cases	80	84	60	47	
Incidence rate (per 1,000 PY*)	24.9	26.7	19.0	14.4	
Multivariate‡ HR* (95% CI*)	1.0 (referent)	1.26 (0.91, 1.74)	0.80 (0.55, 1.17)	0.68 (0.44, 1.04)	0.01
<i>APOE</i> ε4 carriers					
No. of incident cases	26	39	40	35	
Incidence rate (per 1,000 PY)	32.8	42.2	37.1	32.9	
Multivariate‡ HR (95% CI)	1.0 (referent)	1.26 (0.77, 2.09)	1.28 (0.75, 2.18)	1.29 (0.75, 2.22)	0.53
<i>Activity index</i>					
	0–1 activity	2 activities	3 activities	≥4 activities	
<i>All-cause dementia</i>					
<i>APOE</i> ε4 noncarriers					
No. of incident cases	91	81	57	42	
Incidence rate (per 1,000 PY)	37.7	23.0	17.1	12.0	
Multivariate‡ HR (95% CI)	1.0 (referent)	0.78 (0.57, 1.07)	0.70 (0.48, 1.02)	0.44 (0.28, 0.69)	<0.001
<i>APOE</i> ε4 carriers					
No. of incident cases	91	50	42	30	
Incidence rate (per 1,000 PY)	31.7	44.0	41.9	26.0	
Multivariate‡ HR (95% CI)	1.0 (referent)	1.45 (0.81, 2.59)	1.64 (0.90, 2.98)	1.20 (0.63, 2.29)	0.68

\* APOE, apolipoprotein E genotype; PY, person-years; HR, hazard ratio; CI, confidence interval.

† The *p* values for the interaction between leisure-time energy expenditure or activity index with APOE were 0.06 and 0.003, respectively.

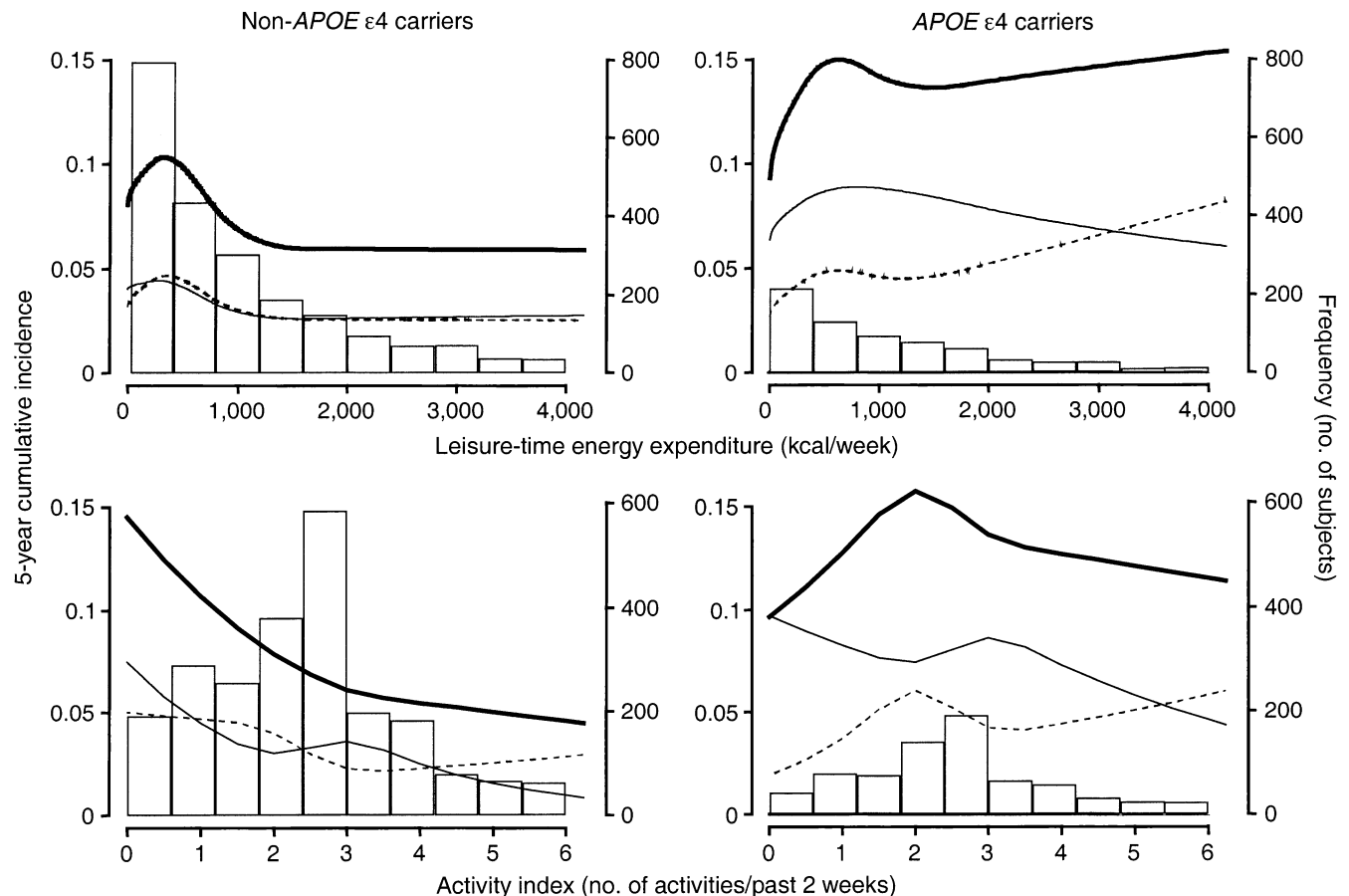
‡ The multivariate model was adjusted for age (continuous), educational level (continuous), gender, ethnicity (Caucasian or non-Caucasian), APOE (ε4 or non-ε4), baseline Modified Mini-Mental State Examination score (continuous), magnetic resonance imaging white-matter-grade score (<3 or ≥3), activities of daily living impairment (<1 or ≥1), instrumental activities of daily living impairment (<1 or ≥1), Lubben Social Network Score (continuous), and social support score (continuous).

or preserve cognitive reserves in the face of cognitive decline via continued use and corresponding cortical and synaptic stimulation of intact neurons (53). In cross-sectional studies, variety of lifestyle activities has been positively associated with indices of cognition among nondemented older women, particularly in the domain of memory (M. Carlson, The Johns Hopkins Medical Institutions, unpublished manuscript).

Alternatively, physical activity may be an index of a healthier lifestyle resulting in less exposure to factors that affect cognitive function and precipitate dementia. In the current study, engaging in a larger number of different activities was generally associated with a more favorable health profile and health behaviors.

In previous studies (54–56), APOE ε4 carriers did not attain the same benefit as noncarriers from physical activity

in terms of blood pressure and lipid patterns. Similarly, our findings suggest differing risk patterns between dementia and physical activity by APOE genotype, and they imply that any potential protective effect associated with physical activity is not enough to overcome the effect of APOE ε4 alleles, or that physical activity and dementia are simply unrelated in persons with APOE ε4 genotypes. However, our findings contrast with a previous study in which an inverse association between physical activity and cognitive decline was observed predominantly in APOE ε4 carriers (13). It is difficult to know whether these findings extend to dementia; not all elderly persons who experience cognitive decline progress to clinical dementia. We note, however, that the interaction between physical activity and APOE ε4 in this study was based on only 28 cases of cognitive decline and



**FIGURE 2.** Five-year cumulative incidence of dementia as a function of leisure-time energy expenditure or activity index among apolipoprotein E genotype (*APOE*)  $\epsilon 4$  carriers and noncarriers, United States, Cardiovascular Health Cognition Study, 1992–2000. Bold curves, all-cause dementia; thin solid curves, Alzheimer's disease; dashed curves, vascular dementia; bars, frequency distribution of physical activity within each *APOE* genotype stratum.

was thus subject to considerable variability. Replication of these findings in larger studies will be required to resolve this apparent discrepancy.

The CHCS is one of the largest prospective studies of older adults with comprehensive information on subclinical and clinical cognitive functioning, dementia status, and cardiovascular factors. In addition, physical activity was collected by using standardized methods (29), and the prospective design of CHCS enabled us to collect information on physical activity in advance of dementia diagnosis, therefore minimizing selection and recall biases.

We did not update the information on physical activity over follow-up because preclinical symptoms may reduce activity levels, compromising the ability to establish temporality. Although misclassification of exposure is possible, all participants in the present analysis were cognitively stable (3MS score >80) at the time that physical activity information was collected. Furthermore, we were able to adjust for baseline 3MS cognitive scores in our analyses. On the basis of these considerations, it is reasonable to suggest that misclassification of exposure would have been nondifferential and would have biased our results toward the null.

Our findings are not without limitations. We were able to assess physical activity levels during older adult life only, but it is unclear during what period of life physical activity is most relevant to preserving cognition and impacting dementia risk. Our finding that number of activities has a stronger association with dementia risk than does kilocalorie expenditure may be an artifact of measurement. Reliability of the Minnesota Leisure Time Activity Questionnaire may be lower at low-to-moderate levels of activity (57), levels at which most older adults participate. It is therefore possible that number of activities may be a more sensitive indicator at these levels. Furthermore, persons with established physical activity habits may be more precise in their recall than persons who exercise sporadically. Similarly, recall of number of activities may be more reliable than specifics about exercise frequency and duration, both factors heavily weighted in calculating total energy expenditure. In this sample, number of activities was significantly and positively correlated with total physical activity energy expenditure. Understanding which components of physical activity reduce dementia risk deserves further attention.

We must also consider the possibility that a reduction in the number of different physical activities is an early symptom of dementia. We addressed this possibility by using several different approaches. First, we excluded all persons with a 3MS score of less than 80 or with prevalent dementia at baseline. However, it is possible that the 3MS is not sensitive enough to detect persons with subclinical dementing illness and that some of these persons were included in our study. Second, we adjusted our analyses for baseline cognitive function, and the inverse association of number of physical activities with dementia risk persisted. Third, we reran the analysis by excluding persons who developed incident dementia within the first year of the follow-up, and the results were essentially unchanged. Furthermore, we used information on physical activity from two time points approximately 5 years apart to obtain a more stable estimate of regular physical activity in older adulthood prior to dementia onset. Finally, we also evaluated the association of physical activity with dementia risk after excluding persons who had one or more difficulties in activities of daily living or instrumental activities of daily living; again, the results were similar.

In summary, this study provides support for the hypothesis that engaging in a number of different physical activities protects against subsequent risk of all-cause dementia, Alzheimer's disease, and vascular dementia over an average 5.4-year follow-up, although the potential benefits of exercise may be limited to APOE  $\epsilon$ 4 noncarriers. Physical activity is already recommended to enhance cardiovascular health and help maintain independence and quality of life in older adults (52). Confirmation of these findings and substantiation of the biologic mechanism by which activity reduces dementia risk may provide an additional impetus for persons to remain or become active in a number of activities in later life.

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