Table 2 *(Continued)*

Association between risk factors and having stiff or painful joints among mid-age women (*n* = 4,780)

1	1.41 (1.24–1.61)	1.35 (1.18–1.54)	1.78 (1.43–2.20)	1.62 (1.30–2.02)
2	1.54 (1.26–1.89)	1.37 (1.11–1.67)	2.67 (2.01–3.54)	2.17 (1.61–2.91)
3	1.93 (1.35–2.75)	1.67 (1.17–2.40)	2.53 (1.55–4.14)	1.96 (1.18–3.25)
4 or more	1.47 (0.77–2.82)	1.10 (0.56–2.14)	3.04 (1.32–7.01)	1.89 (0.79–4.49)
Smoking status				
Never	1.00	1.00	1.00	1.00
Former	1.00 (0.88–1.14)	0.99 (0.87–1.12)	1.23 (1.00–1.54)	1.21 (0.97–1.50)
Current	1.14 (0.95–1.36)	1.08 (0.90–1.30)	1.44 (1.09–1.91)	1.35 (1.01–1.81)
Missing	2.23 (0.63–7.91)	2.11 (0.59–7.60)	2.56 (0.54–12.10)	2.70 (0.55–13.2)
Body mass index				
<20 kg/m^2	1.03 (0.79–1.36)	1.03 (0.78–1.36)	1.22 (0.76–1.95)	1.25 (0.78–2.01)
≥ 20 and <25 kg/m^2	1.00	1.00	1.00	1.00
≥ 25 and <30 kg/m^2	1.10 (0.96–1.27)	1.06 (0.92–1.23)	1.46 (1.15–1.86)	1.36 (1.06–1.74)
≥ 30 kg/m^2	1.63 (1.38–1.92)	1.46 (1.23–1.73)	2.22 (1.73–2.86)	1.83 (1.41–2.38)
Missing	1.32 (1.05–1.66)	1.29 (1.02–1.62)	1.43 (0.98–2.08)	1.35 (0.92–2.00)
Physical activity				
None (<40 MET.min/ week)	1.00	1.00	1.00	1.00
Very low (40 to <300 MET.min/week)	0.86 (0.71–1.05)	0.93 (0.76–1.14)	0.92 (0.67–1.26)	1.08 (0.78–1.49)
Low (300 to <600 MET.min/week)	0.77 (0.63–0.94)	0.88 (0.71–1.08)	0.87 (0.63–1.19)	1.15 (0.82–1.60)
Moderate (600 to <1,200 MET.min/week)	0.82 (0.68–0.99)	0.94 (0.77–1.14)	0.71 (0.52–0.97)	0.91 (0.66–1.27)
High (1,200+ MET.min/ week)	0.75 (0.62–0.90)	0.88 (0.72–1.06)	0.78 (0.58–1.05)	1.06 (0.78–1.45)

[a]Adjusted for all other variables in the table.

Table 3

Association between risk factors and having stiff or painful joints among older women (*n* = 3,970)

	Stiff or painful joints 'sometimes or often' at Time 2		Stiff or painful joints 'often' at Time 2	
Variable at Time 1	Unadjusted odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)	Unadjusted odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)
Education				
Less than high school	1.00	1.00	1.00	1.00
Some high school	0.89 (0.76–1.04)	0.90 (0.76–1.05)	0.86 (0.68–1.09)	0.90 (0.71–1.16)
Completed high school	0.92 (0.74–1.13)	0.97 (0.78–1.20)	1.06 (0.77–1.44)	1.17 (0.85–1.62)
Trade certificate/ university degree	1.01 (0.83–1.23)	1.06 (0.86–1.30)	0.80 (0.59–1.10)	0.93 (0.67–1.28)
Missing	0.89 (0.64–1.24)	0.91 (0.64–1.29)	1.25 (0.79–1.97)	1.37 (0.84–2.22)
Area of residence				
Urban	1.00	1.00	1.00	1.00
Large town	0.94 (0.76–1.16)	0.91 (0.73–1.13)	0.94 (0.67–1.31)	0.88 (0.62–1.24)
Small town/remote area	1.04 (0.91–1.19)	1.02 (0.89–1.18)	1.20 (0.98–1.48)	1.15 (0.93–1.42)
Missing	0.72 (0.42–1.22)	0.75 (0.43–1.29)	0.41 (0.13–1.32)	0.41 (0.12–1.33)
Country of birth				
Australia	1.00	1.00	1.00	1.00
Other English-speaking	0.95 (0.78–1.15)	0.93 (0.76–1.14)	0.87 (0.64–1.18)	0.90 (0.65–1.23)
Non-English speaking	1.00 (0.78–1.29)	0.92 (0.71–1.20)	1.02 (0.70–1.49)	0.90 (0.60–1.34)
Missing	0.94 (0.72–1.23)	0.94 (0.70–1.27)	1.02 (0.68–1.52)	0.91 (0.58–1.42)
Depression				
No	1.00	1.00	1.00	1.00
Yes	1.48 (1.04–2.09)	1.29 (0.90–1.84)	2.15 (1.41–3.29)	1.75 (1.13–2.72)
Number of chronic diseases				
0	1.00	1.00	1.00	1.00

Table 3 *(Continued)*

Association between risk factors and having stiff or painful joints among older women ($n = 3,970$)

1	1.26 (1.08–1.48)	1.23 (1.05–1.44)	1.42 (1.09–1.85)	1.37 (1.05–1.79)
2	1.90 (1.59–2.28)	1.83 (1.52–2.19)	2.09 (1.57–2.77)	1.93 (1.44–2.57)
3	2.43 (1.89–3.14)	2.33 (1.80–3.02)	2.83 (1.99–4.03)	2.53 (1.77–3.63)
4 or more	3.06 (2.12–4.43)	2.93 (2.02–4.26)	5.02 (3.28–7.69)	4.24 (2.74–6.57)
Smoking status				
Never	1.00	1.00	1.00	1.00
Former	1.07 (0.93–1.24)	1.08 (0.93–1.25)	1.22 (0.99–1.52)	1.27 (1.01–1.59)
Current	1.05 (0.78–1.40)	1.10 (0.81–1.49)	1.17 (0.76–1.82)	1.17 (0.75–1.84)
Missing	1.01 (0.77–1.31)	1.04 (0.78–1.37)	1.06 (0.71–1.59)	1.07 (0.70–1.64)
Body mass index				
<20 kg/m^2	1.04 (0.72–1.48)	0.97 (0.67–1.39)	0.98 (0.54–1.77)	0.86 (0.47–1.58)
≥ 20 and <25 kg/m^2	1.00	1.00	1.00	1.00
≥ 25 and <30 kg/m^2	1.46 (1.26–1.70)	1.39 (1.19–1.63)	1.46 (1.15–1.84)	1.33 (1.04–1.68)
≥ 30 kg/m^2	1.42 (1.14–1.77)	1.26 (1.00–1.58)	1.68 (1.23–2.31)	1.32 (0.95–1.84)
Missing	1.13 (0.92–1.39)	1.07 (0.87–1.32)	1.52 (1.13–2.05)	1.36 (1.00–1.85)
Physical activity				
None (<40 MET.min/ week)	1.00	1.00	1.00	1.00
Very low (40 to <300 MET.min/week)	0.98 (0.80–1.22)	1.04 (0.84–1.29)	0.87 (0.65–1.17)	0.94 (0.70–1.27)
Low (300 to <600 MET.min/week)	1.00 (0.83–1.20)	1.11 (0.92–1.34)	0.63 (0.48–0.82)	0.72 (0.55–0.96)
Moderate (600 to <1,200 MET.min/week)	0.80 (0.65–0.98)	0.89 (0.72–1.10)	0.48 (0.34–0.67)	0.54 (0.39–0.76)
High (1,200+ MET.min/ week)	0.83 (0.69–0.99)	0.94 (0.78–1.14)	0.51 (0.38–0.68)	0.61 (0.46–0.82)

[a]Adjusted for all other variables in the table.

[9]. More precise measures of occupational physical activity are required to further explore these associations.

We did not observe a statistically significant association between physical activity and self-reported stiff or painful joints 'sometimes or often' in either cohort. This finding may reflect a wider variability in interpretation of the phrase 'sometimes' than 'often,' with some respondents exaggerating the frequency of their symptoms by selecting 'sometimes' when symptoms occurred 'rarely,' resulting in a weakened ability to detect an association.

The present study was the first to assess the prospective association between physical activity and symptoms of arthritis in two different age cohorts of women. Our observation of no statistically significant associations in three of the four multivariable analyses supports the results of prospective studies that have assessed the long-term associations between physical activity and arthritis in other large cohorts of women [5,7]. In a 25-year cohort study that included 4,073 women 20–87 years of age, Cooper Clinic (US) researchers [7] reported no statistically significant association between walking or jogging and self-reported physician-diagnosed hip and knee osteoarthritis for women after controlling for BMI, alcohol, smoking status, and caffeine consumption. In the 20-year Alameda County Cohort Study (US) [5], no statistically significant association between leisure-time physical activity and self-reported arthritis was seen among the 1,148 women who participated (mean age = 43 years for all participants) after controlling for age, race, BMI, and the presence of five or more depressive symptoms. Assessment of the risk factors for radiographic knee osteoarthritis among 715 mid-age women (aged 54 ± 6 years) in the Chingford Study Cohort (UK) [9] revealed that walking, occupational physical activity, and sport were not statistically significantly associated with incident osteophytes over 4 years after adjusting for age, social class, BMI, and smoking status among other factors – only walking was associated with decreased odds of joint space narrowing (OR = 0.38, 95% CI = 0.15–0.93) over that same time period after adjusting for the same variables.

Our finding that physical activity is protective against complaints of stiff or painful joints 'often' in older women does not support the results from these other studies [5,7-9]. Only the Framingham Study [8], however, focused specifically on older women. In that study, the researchers found an *increased* risk of radiographic knee osteoarthritis over 10 years (but not after 20 or 40 years) among the 69 older women (mean age = 71 ± 5 years for the sample of men and women) in the highest quartile of physical activity in a model adjusted for age, BMI, cigarette smoking, and other covariates (OR = 3.1, 95% CI = 1.1–8.6). In contrast, our results showed a clear dose–response relationship between physical activity and incident stiff or painful joint 'often' over 3 years in women aged 72–79 years at T1.

Interpretation of our results in the context of the findings from other studies should be made with caution because each study of the risk factors for arthritis has used a different measure of physical activity. In our study, a generic physical activity score reflected participation in walking as well as moderate-intensity and vigorous-intensity leisure-time activities during the past week, whereas other studies have used 24-hour recall [8], have focused on specific physical activities, such as walking [7,9], or have used their own physical activity index to evaluate habitual leisure-time physical activity [5]. Moreover, the outcomes of each study differed. While our study examined arthritis symptoms, other studies assessed self-reported arthritis [5], self-reported osteoarthritis [7], or radiographic osteoarthritis [8,9]. It should also be noted that different studies used follow-up periods ranging from 4 to 40 years [5,7-9]. Although our follow-up period of 3 years was short, it was appropriate for assessing the development of symptoms of arthritis rather than arthritis itself, which can take much longer to develop.

Our study does not provide insight into the mechanisms by which physical activity may impact development of arthritis symptoms in older women; however, the constellation of significant factors (physical activity, BMI, and smoking) supports the suggestion that there is a metabolic basis to the development of arthritis [9]. Alternatively, the links between physical activity and arthritis symptoms might be explained by exercise-related endorphin release, by protection against fibromyalgia, by increased resistance to musculoskeletal injury, by differences in pain threshold for people who exercise regularly, or by other psychological mechanisms [37].

Unique to the present study, risk factors for arthritis symptoms were examined separately in mid-age women and in older women, which allowed us to detect age-related differences in the association between physical activity and stiff or painful joints. Other strengths of this study were that it included a large population-based sample of women and used a prospective design. Women in each cohort who reported stiff or painful joints 'sometimes' or 'often' at T1 were excluded to reduce the possibility of reverse causation (that is, women became inactive because they had stiff or painful joints). Other strengths were that we used a validated and reliable measure of physical activity [25-27] and that we provided evidence of the predictive validity for our stiff and painful joints measure against self-reported physician-diagnosed arthritis and physical functioning.

A major limitation of this study was that all the data were self-reported. We did not have radiological or clinical measures, so we chose to focus on symptoms rather than on clinically diagnosed arthritis. This provided the opportunity to include women who may not have yet sought medical care or not yet been diagnosed with the problem. While it could be argued that the question about symptoms lacks specificity and sensitivity when compared with more objective measures, other researchers have shown that reporting these symptoms is associated with decreased ability to conduct functional tasks and with disability [38]. Previous studies have also shown that people underreported confirmed diagnoses when asked to report physician-diagnosed osteoarthritis, indicating that the burden of arthritis in the population has been underestimated [7,39].

Another limitation is the potential effect of participation bias on the results. Although the ALSWH included a fairly representative national sample of mid-age women and older women at the first data collection point [21], as with all prospective studies, there is continual attrition over time, with a tendency for more healthy women to remain in the cohort [40]. This 'healthy' participation bias was further exaggerated here by our inclusion of only women who did *not* report having stiff or painful joints 'sometimes' or 'often' at T1. While this was done to reduce the possibility of reverse causation (as described above), the original participation bias, together with the selection bias of women without joint pain or stiffness and exclusion of women with missing physical activity data, meant that our samples were more physically active than the general population of mid-age women and older women. The findings cannot, therefore, be generalized to all women in these age groups.

We were unable to examine factors associated with specific sites of the joint symptoms (for example, knee versus wrist), or about the year when the stiff or painful joint symptoms first developed, precluding the use of survival analysis or other procedures that require the exact duration of follow-up to be known. Finally, because few women in the ALSWH cohorts reported levels of physical activity that would be typically associated with 'athletic' training, we were unable to confirm findings from previous studies indicating that competitive sport and associated injuries might be involved in the development of osteoarthritis [8,10].

Conclusion

The prevalence of arthritis in Australia is rapidly approaching that of cardiovascular disease [2]. As the cost to the Australian healthcare system of managing arthritis and its symptoms is likely to be greater than for other prominent health problems such as diabetes and asthma [2], the identification of physical inactivity as a potentially modifiable risk factor of incident stiff or painful joints among older women is important. Indeed, if preventive intervention strategies, such as increasing physical activity participation by even small amounts, could delay the onset and development of symptoms of arthritis, there could be considerable cost savings to the healthcare system and to older women themselves, not to mention reductions in pain and suffering caused by this often debilitating health problem.

Competing interests

The authors declare that they have no completing interests.

Authors' contributions

KCH and YDM participated in the study conception and design, statistical analyses, interpretation of the data, and drafting of the manuscript. WJB participated in the study conception, study design, data acquisition, interpretation of the data, and drafting of the manuscript. All authors have read and approved the final manuscript.

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論文名	Relationship between physical activity and stiff or painful joints in mid-aged women and older women: a 3-year prospective study
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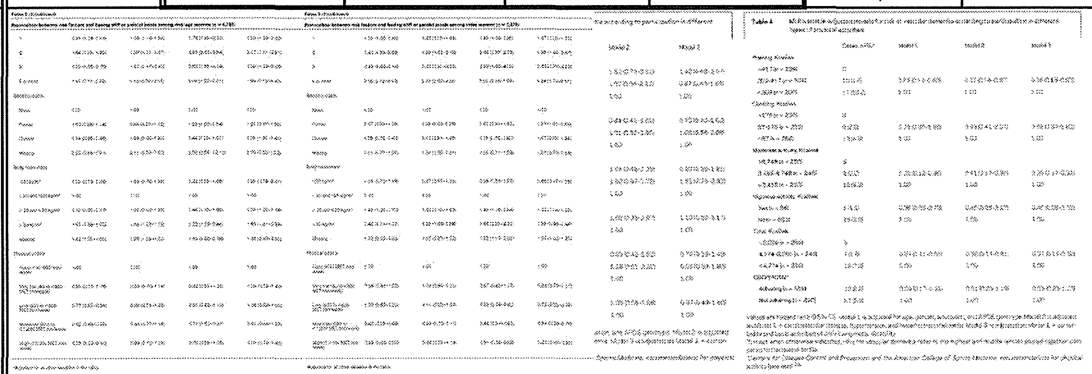
		ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象の内訳	対象	一般健常者	空白		( )		コホート研究
	性別	女性	( )		( )		( )
	年齢	52.53±1.49歳、	[redacted]		( )		前向き研究
	対象数	5000～10000			( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	な し	な し	介護予防	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表



図表掲載箇所	P8of13, Table2, P10of13, Table3
概 要（800字まで）	本研究は、オーストラリアのThe Australian Longitudinal Study on Women's Health(ALSWH)に参加した中年女性4,780名と高齢女性3,970名を対象に3年間の追跡調査を行い、身体活動量と関節痛発症リスクの関連を検討したものである。ベースライン測定時に、身体活動量について、過去1週間のうち、通勤や余暇時間の速歩、中強度余暇身体活動、高強度余暇身体活動に費やした時間と頻度を尋ね、それらの合計により総身体活動量を得た。身体活動量は、None(40メッツ分/週未満)、Very low(40-300メッツ分/週)、Low(300-600メッツ分/週)、Moderate(600-1200メッツ分/週)、High(1200メッツ分/週以上)の5群に分類した。また、ベースライン時、3年後測定時に過去1年間に関節のこわばりや痛みを感じた経験を尋ね、ときどき、しばしばの2群に分類した。高齢女性において、関節痛発症がときどきと答えた集団では身体活動との関連はみられなかったが、関節痛発症がしばしばと答えた集団では、身体活動量がLow、Moderate、Highの集団で関節痛発症リスクがそれぞれ0.72(95%信頼区間:0.55-0.96)、0.54(0.39-0.76)、0.61(0.46-0.82)と有意に減少した。中年女性においては、いずれも差はみられなかった。
結 論（200字まで）	高齢女性において、身体活動量と関節痛発症リスクに量反応的な関連が明らかとなった。
エキスパートによるコメント（200字まで）	身体活動基準の策定に使用された研究である。高齢女性において、少ない身体活動量と高い関節痛発症リスクに量反応的な関連が明らかにした点に意義がある。ロコモに対する身体活動の予防効果について今後の研究が期待される。

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Physical activity and dementia risk in the elderly

Findings from a prospective Italian study

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ABSTRACT

Objective: To examine the effect of physical activity on risk of developing Alzheimer disease (AD) and vascular dementia (VaD) in the elderly.

Methods: Data are from a prospective population-based cohort of 749 Italian subjects aged 65 and older who, in 1999/2000, were cognitively normal at an extensive assessment for clinically overt and preclinical dementia and, in 2003/2004, underwent follow-up for incident dementia. Baseline physical activity was measured as energy expenditure on activities of different intensity (walking, stair climbing, moderate activities, vigorous activities, and total physical activity).

Results: Over 3.9 ± 0.7 years of follow-up there were 86 incident dementia cases (54 AD, 27 VaD). After adjustment for sociodemographic and genetic confounders, VaD risk was significantly lower for the upper tertiles of walking (hazard ratio [HR] 0.27, 95% CI 0.12 to 0.63), moderate (HR 0.29, 95% CI 0.12 to 0.66), and total physical activity (HR 0.24, 95% 0.11 to 0.56) compared to the corresponding lowest tertile. The association persisted after accounting for vascular risk factors and overall health status. After adjustment for sociodemographic and genetic confounders, AD risk was not associated with measures of physical activity and results did not change after further adjustment for vascular risk factors and overall health and functional status.

Conclusions: In this cohort, physical activity is associated with a lower risk of vascular dementia but not of Alzheimer disease. Further research is needed about the biologic mechanisms operating between physical activity and cognition. *Neurology*® **2008;70:1786-1794**

GLOSSARY

ACSM = American College of Sports Medicine; **AD** = Alzheimer disease; **ADL** = activities of daily living; **CDCP** = Centers for Disease Control and Prevention; **CSBA** = Conselice Study of Brain Ageing; **GDS** = Geriatric Depression Scale; **HR** = hazard ratio; **IADL** = instrumental activities of daily living; **MCI** = mild cognitive impairment; **MDB** = Mental Deterioration Battery; **MMSE** = Mini-Mental State Examination; **VaD** = vascular dementia.

Regular physical activity is important for health promotion and might be an effective strategy to prevent dementia onset.[1] Observational[2,3] and intervention studies[1,4,5] consistently showed an association between physical exercise and better cognitive performance in selected samples of older adults, although not all investigations confirmed this finding.[6,7]

Longitudinal investigations of the effect of physical activity on dementia risk in elderly persons are fewer in number and produced inconsistent results. A lower risk of all-cause dementia and Alzheimer dementia (AD) among subjects regularly practicing low-to-medium intensity physical activities was found in some population-based studies[8-14] but not in others.[15-18] Moreover, only a few investigations examined the effect of physical activity on vascular dementia (VaD) risk[10,11,13,18] and none reported an association.

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In this study, data from an elderly Italian population-based cohort were used to examine the association between different measures of physical activity and 4-year risk of all-cause dementia, AD, and VaD.

METHODS Subjects. Data are from the Conselice Study of Brain Ageing (CSBA), a population-based study of elderly Italian individuals aimed to investigate epidemiology and risk factors for cognitive impairment. CSBA design and methods have been described in detail elsewhere.[19] The study was approved by the Institutional Review Board of the Department of Internal Medicine, Cardioangiology, and Hepatology, University of Bologna; written informed consent was obtained from all participants.

Briefly, in 1999 to 2000, 1,016 (75%) of the 1,353 individuals at least 65 years old residing in the Italian municipality of Conselice (province of Ravenna, Emilia Romagna region) participated in the prevalence study. Since the 1950s Conselice has been a wealthy urban area and its actual economy is mainly based on industry and handicraft, but the older inhabitants were raised and lived in a rural environment most of their youth. The occupation most often held in this cohort was farmer/housewife (47.8%), followed by blue collar (34.3%), and white collar (17.9%). Thirty-three out of the 34 subjects of the study population known to live in nursing homes participated in the prevalence study. As previously reported,[19] incidence rate per 1,000 person-years in the CSBA cohort was 37.8 (95% CI 30.0 to 47.7) for any dementia, 23.8 (95% CI 17.3 to 31.7) for AD, and 11.0 (95% CI 7.2 to 16.9) for VaD. These rates are similar to those reported for other European and US studies of older, low-educated rural cohorts.[19]

Measurement of physical activity. Information on physical activity was collected at baseline by trained interviewers using the Paffenbarger Physical Activity Questionnaire.[20] Participants were asked 1) how many city blocks (or the equivalent: 12 block = 1 mile) they walked each day for exercise or as a part of their normal routine and about their usual outdoor walking pace; 2) how many flights of stairs they climbed each day; 3) about frequency and duration of their participation per week during the past year in any other occupational, recreational, or sport activity. According to its intensity, each activity was assigned a metabolic equivalent (mL of used O_2/minute, MET, where 1 MET is proportional to the energy expended while sitting quietly) and the corresponding energy expenditure (kilocalories/week) was calculated. The measures of physical activity used for this study were as follows: energy expenditure per week in walking (from 2.5 to 4.5 METs according to pace), stair climbing (8 METs), any other moderate (3 to 6 METs) or vigorous (>6 METs) activity, and total physical activity (sum of energy expenditure in all the previously listed physical activities). Additionally, participants were classified according to whether they adhered to the recommendation for physical activity (30 minutes or more of moderate-intensity physical activity on at least 4 days per week) issued by the Centers for Disease Control and Prevention and the American College of Sports Medicine (CDCP/ACSM).[21] The moderate activities most frequently reported in the CSBA cohort were house and yard work, gardening, light carpentry, and bicycling on level ground. The most frequently reported vigorous activities were farming and heavy carpentry. Less than 1% of the cohort reported regular participation in sports activities or recreational group physical activities involving a social interaction (e.g., ballroom dancing).

Case finding. A two-phase procedure was used during 1999 to 2000, consisting of a cognitive screening phase and an extensive neuropsychological assessment of those positive at screening in order to identify mild cognitive impairment (MCI) and dementia cases. The screening phase included 1) a standardized personal interview for collection of data on sociodemographic characteristics, lifestyle, medical history, ability to perform basic activities of daily living (ADL)[22] and instrumental activities of daily living (IADL),[23] evaluation of depressive symptoms with the Geriatric Depression Scale (GDS),[24] and measurement of global cognitive function with the Italian version of the Mini-Mental State Examination (MMSE),[25] for which standardized age- and education-specific coefficients are available[26]; 2) a standardized medical and neurologic examination; and 3) collection of fasting venous blood samples. Whenever available, previous medical records were reviewed. For subjects unable to answer because of physical or mental impairments, information was obtained from relatives and general practitioners. Subjects with MMSE score below 24 were considered positive at cognitive screening and underwent further neuropsychological assessment with the Mental Deterioration Battery (MDB).[27] MDB includes tests for evaluation of memory (immediate and delayed recall of Rey's 15 words), language (sentence construction), frontal function (phonological word fluency), abstract reasoning (Raven's 47 progressive colored matrices), and visuospatial abilities (freehand copying of drawings and copying of drawings with landmarks). MDB is validated for use in rural and poorly educated Italian subjects. Memory was additionally tested using the prose memory test.[28] All of these tests are provided with standardized thresholds for the definition of impairment in the corresponding cognitive domain (score ≤1.5 SD the mean for a reference adult Italian population-based cohort), and age- and education-specific coefficients to be applied to the subject's raw score before comparison with the corresponding threshold.

Subjects with MMSE below 10 did not receive further neuropsychological testing. Whenever recent neuroradiologic data were not available, the subject was scheduled for a noncontrast CT brain scan. Standardized information about functional and mental status of subjects positive at cognitive screening was also obtained from a collateral informant (a relative or any other person with a reliable knowledge of the individual, including the subject's medical practitioner). Dementia was diagnosed with Diagnostic and Statistical Manual of Mental Disorders–IV clinical criteria,[29] AD with National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria,[30] VaD with National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria.[31] Diagnoses were independently made by two physicians who were blinded to the Paffenbarger questionnaire's results.

The definition of MCI evolved after the CSBA started and current international MCI consensus criteria[32] were retrospectively adapted to diagnose cases. A MCI diagnosis was given to all subjects scoring <24 at MMSE who 1) had age- and education-adjusted score ≤1.5 SD below the reference threshold at any of the tests used for neuropsychological evaluation; 2) were able to independently perform ADL and IADL (limitations due to motor impairments were not taken into account for this criterion); 3) did not meet clinical criteria for dementia.[29]

Subjects with major sensory-motor deficits or any psychiatric condition other than dementia deemed to hamper a reliable cognitive assessment, and for whom we could not ascertain whether there had actually been a decline from a previously higher functioning level, were diagnosed as cognitively unclassifiable.

Identification and differential diagnosis of dementia incident cases in 2003 to 2004 followed the same two-phase procedure used to identify prevalent cases. Additionally, information reliable enough to establish or exclude a dementia diagnosis was sought for deceased and refusers.

Laboratory. Plasma tHcy was measured by the fully automatized IMx assay (Abbott laboratories, Abbott Park, IL). Hyperhomocysteinemia was defined as plasma tHcy > 15 μmol/L, corresponding to the standard definition for hyperhomocysteinemia by international consensus.[33] Genomic DNA was obtained from EDTA-treated blood using a commercial DNA extraction kit (QiAmp blood kit; Kaga, Crawley, UK). APOE ε allele genotyping was performed by PCR as previously described.[34] Subjects were categorized into those with and without an APOE ε4 allele.

Covariates. Covariates were defined using data collected at baseline. Educational status was categorized as 3 vs 4 or more years of formal education, because at the time the CSBA participants went to school the first educational degree was achieved after 3 years of schooling.

Comorbidity was defined as the concurrent presence of two or more of the following medical conditions: hypertension, cardiovascular disease (history of myocardial infarct and congestive heart failure), cerebrovascular disease (history of stroke or TIA), diabetes, chronic pulmonary disease, and cancer. Hypertension was defined as blood systolic pressure $\geq$130 mm Hg, blood diastolic pressure $\geq$85 mm Hg (using the average of two seated measurements), or currently using an antihypertensive medication. All other diagnoses were based on medical history as provided by the participants and their medical practitioners, including revision of available medical records. ADL motor disability was defined as need for help in performing one or more of the corresponding daily living activities because of motor impairment.

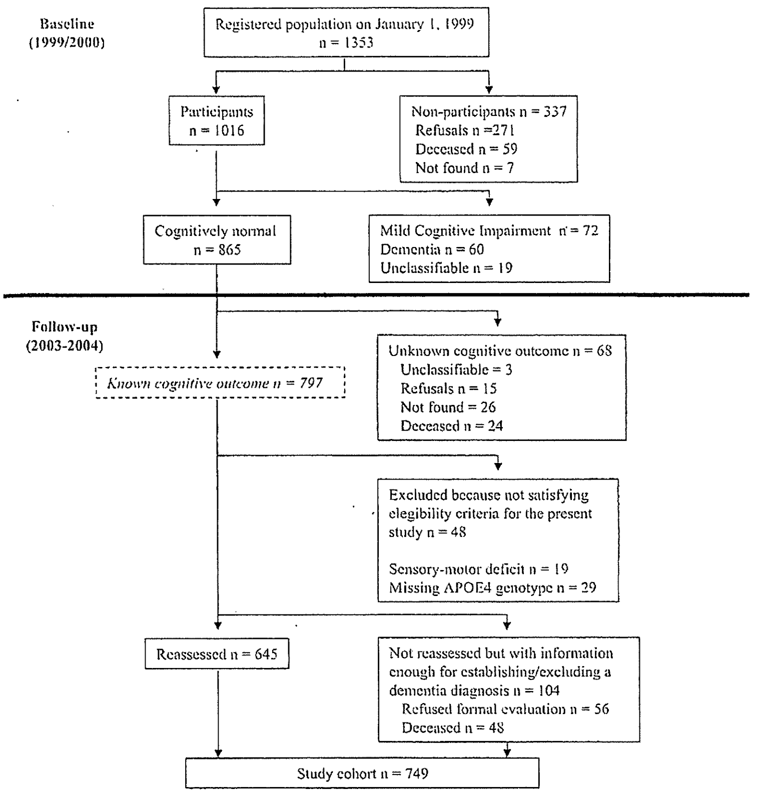
Statistical analysis. Variables are presented as mean ± SD (continuous) or number and percentage (categorical). Continuous variables were compared using independent-samples t test and categorical variables using the χ^2 test. Physical activity measures had a skewed distribution and were all categorized into tertiles of weekly energy expenditure except for vigorous physical activity, which was dichotomized as a yes/no variable due to the scant number of subjects practicing it. Cox proportional-hazard regression models were used to estimate hazard ratios (HR) for incident all-cause dementia, AD, and VaD across levels of physical activity. Three set of multivariate models were used. In a first model, HRs were adjusted for sociodemographic and genetic confounders (age, gender, education, and APOE genotype). In a second model, HRs were adjusted for all the confounders of model 1 plus a set of vascular risk factors (cardiovascular disease, hypertension, and hyperhomocysteinemia) that might be either confounders or intermediates in the relationship. In a third model, HRs were adjusted for all the confounders of model 1 plus a set of variables related to baseline general physical (comorbidity) and functional status (ADL motor disability), in order to examine the hypothesis that any association between physical activity and incident dementia was just a marker of better overall health status. For all measures of physical activity categorized into tertiles, the bottom one was used as the reference category. Because of to the scant number of VaD cases and preliminary analyses showing that VaD incidence did not significantly differ between the middle and the highest tertile of each measure, Cox analyses for VaD were performed on the upper tertiles pooled together. To minimize the deleterious effects of overadjustment, we did not include MMSE in the Cox models, because this variable was used in the dementia workup.[35]

RESULTS We excluded from the present investigation all CSBA participants who had a baseline diagnosis of MCI (n = 72), dementia (n = 60), or unclassifiable cognitive status (n = 19). We also excluded all participants who had sensory/motor deficits precluding any outdoor activity (n = 19), did not have APOE4 genotyping (n = 29), or lacked follow-up information about cognitive status reliable enough to establish or exclude a dementia diagnosis (n = 68). The final sample included 749 subjects (see flow chart in the figure for further details). Not included CSBA participants were older and less educated than the study cohort but did not differ for gender.

During a mean of 3.9 ± 0.7 years of follow-up, 86 incident dementia cases (54 AD, 27 VaD, 5 cases from other dementia) occurred in the study cohort. Five cases were identified among subjects with adjusted follow-up MMSE score $\geq$ 24, because the patients had already received a diagnosis of mild dementia.[18] All VaD cases had neuroimaging evidence of brain infarction. Table 1 reports the cohort's baseline characteristics. Compared to participants who did not develop dementia, incident dementia cases were older, were less educated, were more frequently women, had a lower MMSE score, and were more likely to have hyperhomocysteinemia, ADL motor impairment, and comorbidity (table e-1 on the *Neurology*® Web site at www.neurology.org).

Participants reported a wide range of weekly energy expenditure: 0 to 8,344 Kcal/week for walking; 0 to 2,016 Kcal/week for stair climbing; 0 to 15,508 Kcal/week for moderate physical activity; 0 to 15,876 Kcal/week for vigorous physical activity; and 0 to 18,348 Kcal/week for total physical activity. About 23.2% of participants never walked for exercise or daily activities. About 21.2% reported no stair climbing activity. Only

Figure Flow chart detailing the derivation of the incidence study sample



3.9% reported no performance of moderate physical activity in the previous year, whereas 87.8% reported no performance of vigorous activity in the same interval. Less than 1% of the study participants reported to be completely sedentary, but only 38% were physically active according to the CDCP/ACSM recommendations.

Table 2 reports the results for risk of any dementia across different levels of physical activity. After adjusting for sociodemographic and genetic confounders, risk of any dementia was significantly lower for the highest tertile of moderate physical activity (p for trend = 0.037) and total physical activity (p for trend = 0.020) compared to the corresponding lowest tertile. However, both associations disappeared after further adjustment for vascular risk factors and overall health status.

No significant association with risk of any dementia was found for the other measures of physical activity. Table 3 reports multivariable-adjusted results for risk of AD across different levels of physical activity. No significant association was found between physical activity and AD risk, independently of any adjustment. Results did not change after exclusion of five subjects with a diagnosis of AD with cerebrovascular disease according to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria.[31] Table 4 reports multivariable-adjusted results for risk of VaD across different levels of physical activity. After taking into account sociodemographic and genetic confounders, VaD risk was significantly lower for the upper tertiles of walking, moderate physical activity, and total physical activity compared to the corresponding lowest tertile. In the same model, VaD risk was not associated with vigorous physical activity but was lower in participants adhering to the CDCP/ACSM recommendations compared to those who did not. None of these associations was affected by further adjustment for vascular risk factors or overall health status, except for adherence to CDCP/ACSM recommendations, which lost significance.

Additional adjustment for other available variables (body mass index, serum cholesterol, GDS, IADL motor impairment) did not affect the study results (data not shown).

Table 1 Baseline characteristics of the study cohort

	Participants, n = 749
Age, y, mean ± SD	73.2 ± 6.0
Women, n (%)	401 (53.5)
Education ≤3 y, n (%)	211 (28.1)
APOE ε4 carriers, n (%)	123 (16.4)
Cardiovascular disease, n (%)	132 (17.6)
Hypertension, n (%)	549 (73.7)
Hyperhomocysteinemia, n (%)	187 (24.9)
Mini-Mental State Examination score, mean ± SD	28.2 ± 1.5
Basic activities of daily living motor disability, n (%)	149 (19.9)
Comorbidity, n (%)	217 (29.0)

DISCUSSION In this Italian elderly cohort, higher levels of energy expenditure in walking, moderate physical activity other than walking, and total physical activity were associated with a lower VaD risk independent of several sociodemographic, genetic, and medical confounders. By contrast, no beneficial effect of physical activity was found on AD risk.

The following, not mutually exclusive, hypotheses have been proposed to explain how cognition may benefit from physical activity.[2-4] First, physical activity may improve cerebral blood flow and lower the risk of cerebrovascular disease. Second, physical activity may stimulate synaptic plasticity, secretion of trophic factors,

Table 2 Multivariable-adjusted models for risk of any dementia according to participation in different types of physical activities

	Cases, n (%)	Model 1	Model 2	Model 3
Walking, Kcal/wk				
>417 (n = 239)	17 (7.1)	0.60 (0.33–1.12)	0.69 (0.37–1.28)	0.67 (0.36–1.25)
209–417 (n = 304)	30 (9.9)	0.67 (0.37–1.09)	0.87 (0.52–1.46)	0.74 (0.45–1.22)
<209 (n = 206)	39 (18.9)	1.00	1.00	1.00
Stair climbing, Kcal/wk				
>175 (n = 250)	20 (8.0)	0.73 (0.42–1.28)	0.80 (0.46 - 1.40)	0.74 (0.43–1.30)
57–175 (n = 233)	26 (11.2)	1.02 (0.61–1.70)	1.09 (0.65 - 1.83)	1.04 (0.62–1.73)
<57 (n = 266)	40 (15.0)	1.00	1.00	1.00
Moderate activity, Kcal/wk				
>6,749 (n = 250)	19 (7.6)	0.51 (0.28–0.95)	0.67 (0.36–1.25)	0.58 (0.32–1.06)
3,455–6,749 (n = 246)	33 (13.4)	0.86 (0.52–1.42)	1.10 (0.66–1.83)	0.91 (0.55–1.50)
<3,455 (n = 253)	34 (13.4)	1.00	1.00	1.00
Vigorous activity, Kcal/wk				
Yes (n = 86)	5 (5.5)	0.64 (0.25–1.62)	0.71 (0.28–1.80)	0.68 (0.27–1.73)
No (n = 663)	81 (12.3)	1.00	1.00	1.00
Total activity, Kcal/wk				
>8,090 (n = 250)	19 (7.6)	0.52 (0.29–0.93)	0.68 (0.37–1.23)	0.58 (0.32–1.06)
4,774–8,090 (n = 249)	26 (10.4)	0.63 (0.38–1.05)	0.80 (0.47–1.38)	0.69 (0.41–1.15)
<4,774 (n = 250)	41 (16.4)	1.00	1.00	1.00
CDCP/ACSM*				
Adhering (n = 459)	42 (9.2)	0.67 (0.43–1.06)	0.81 (0.51–1.28)	0.73 (0.46–1.15)
Not adhering (n = 290)	44 (15.2)	1.00	1.00	1.00

Values are hazard ratio (95% CI). Model 1 is adjusted for age, gender, education, and APOE genotype. Model 2 is adjusted as Model 1 + cardiovascular disease, hypertension, and hyperhomocysteinemia. Model 3 is adjusted as Model 1 + comorbidity and basic activities of daily living motor disability.
*Centers for Disease Control and Prevention and the American College of Sports Medicine, recommendations for physical activity (see text).[21]

neurotransmitter synthesis, and neurogenesis, providing cognitive reserves against brain damage. Third, physical activity may decrease secretion of brain-toxic stress hormones like cortisol. Finally, more than from exercise itself, the beneficial effects of physical activity on cognition might result, all or in part, from the mental and social stimulation related to an active lifestyle.

Some studies found a strong association between physical activity and AD risk[8-14] whereas, in agreement with the present investigation, others did not.[15,18] However, because of the width of the CIs for AD found in the CSBA study, it cannot be excluded that significant results for this dementia subtype may have been missed by lack of statistical power. Therefore, we caution the reader against concluding that this study provides definite evidence that AD is not preventable thorough exercise. Moreover, differently from many other population-based cohorts,[9,11,16,18] CSBA participants had a very low rate of participation in sports or group exercise and their usual physical activities reflected their rural upbringing and poor educational background. Therefore, we cannot exclude that other types of physical activities may actually protect against AD, and our results might even indirectly support the hypothesis that lack of social and intellectual engagement counteracts the beneficial effect of physical activity on AD risk.[2,15,17]

No effect of physical activity on VaD risk was reported in the few studies of this issue.[10,11,13,18] In the CSBA cohort, by contrast, walking and moderate physical activity other than walking were both associated with a lower VaD risk whereas no association was found for stair climbing and other vigorous activities. It is important to note that, in terms of lowering VaD risk, an easy-to-perform moderate activity like walking provided the same benefits of other, more demanding activities of similar intensity, and being in the upper tertiles of total weekly energy expenditure did not offer any specific additional advantage. The study also showed that, when measuring physical activ-

Table 3	Multivariable-adjusted models for risk of Alzheimer dementia according to participation in different types of physical activities		

	Cases, n (%)	Model 1	Model 2	Model 3
Walking, Kcal/wk				
>417 (n = 239)	17 (7.1)	1.37 (0.67–2.83)	1.52 (0.73–3.12)	1.42 (0.68–2.97)
209–417 (n = 304)	30 (9.9)	0.86 (0.45–1.66)	1.07 (0.54–2.12)	0.87 (0.45–1.69)
<209 (n = 206)	39 (18.9)	1.00	1.00	1.00
Climbing, Kcal/wk				
>175 (n = 250)	20 (8.0)	0.80 (0.40–1.60)	0.84 (0.42–1.69)	0.79 (0.40–1.60)
57–175 (n = 233)	26 (11.2)	1.08 (0.56–2.07)	1.01 (0.52–1.95)	1.08 (0.56–2.08)
<57 (n = 266)	40 (15.0)	1.00	1.00	1.00
Moderate activity, Kcal/wk				
>6,749 (n = 250)	19 (7.6)	0.81 (0.36–1.82)	1.04 (0.46–2.35)	0.80 (0.35–1.81)
3,455–6,749 (n = 246)	33 (13.4)	1.53 (0.79–2.96)	1.90 (0.97–3.73)	1.51 (0.78–2.92)
<3,455 (n = 253)	34 (13.4)	1.00	1.00	1.00
Vigorous activity, Kcal/wk				
Yes (n = 86)	4 (4.4)	0.93 (0.32–2.68)	1.02 (0.35–2.97)	1.10 (0.38–3.17)
No (n = 663)	50 (7.6)	1.00	1.00	1.00
Total, Kcal/wk				
>8,090 (n = 250)	13 (5.2)	0.71 (0.34–1.49)	0.89 (0.42–1.92)	0.70 (0.33–1.49)
4,774–8,090 (n = 249)	20 (8.0)	0.94 (0.50–1.77)	1.16 (0.61–2.22)	0.95 (0.50–1.80)
<4,774 (n = 250)	21 (8.4)	1.00	1.00	1.00
CDCP/ACSM*				
Adhering (n = 459)	42 (9.2)	0.88 (0.50–1.57)	1.05 (0.58–1.88)	0.87 (0.49–1.60)
Not adhering (n = 290)	44 (15.2)	1.00	1.00	1.00

Values are hazard ratio (95% CI). Model 1 is adjusted for age, gender, education, and APOE genotype. Model 2 is adjusted as Model 1 + cardiovascular disease, hypertension, and hyperhomocysteinemia. Model 3 is adjusted as Model 1 + comorbidity and basic activities of daily living motor disability.
*Centers for Disease Control and Prevention and the American College of Sports Medicine, recommendations for physical activity (see text).[21]

ity only in terms of adherence to the CDCP/ACSM recommendations, the association with lower VaD risk was not an independent one but might just mirror the better health profile associated with an active lifestyle. This finding may be important for the choice of physical activity measures in future studies attempting to define strategies for prevention of cognitive impairment in the elderly.

Comparison of our findings with those from previous studies is hindered by several methodologic differences. First, while some investigations used data from already well-characterized population-based cohort surveys focused on aging,[9,11,16,18] others focused on population subsets with peculiar features (members of a same health care system implementing exercise promotion strategies,[14] urban-only samples,[8,12,15] subjects from a specific ancestry[13]). Another problematic issue is how physical activity was measured in previous investigations. Most authors did not quantify energy expenditure, but simply recorded if the subjects reported practicing a few selected types of physical activities,[9,10,12] practicing outdoor activities as compared to being limited to indoor ones,[8] or exercising three or more times per week at an intensity greater than walking.[11,14] In the only study where energy expenditure was actually measured,[2] estimates were significantly lower than those for activities of the same intensity in the CSBA cohort, suggesting that the beneficial effects of physical activity on VaD risk found in this cohort might depend on a threshold effect. All studies controlled for demographics and education, but only a few also controlled for vascular risk factors, physical function, and health status.[11,13,17,18]

APOE genotype is a risk factor for both late onset AD and VaD[36] and it has been suggested to modify the effect of physical activity on cognition, with the benefits of an active lifestyle alternatively reported as limited to noncarriers[18] and carriers.[37] No similar effect of APOE genotype was found in the CSBA cohort, but we cannot

Table 4	Multivariable-adjusted models for risk of vascular dementia according to participation in different types of physical activities			
	Cases, n (%)*	Model 1	Model 2	Model 3
Walking, Kcal/wk				
>417 (n = 239)	0			
209-417 (n = 304)	10 (1.8)	0.27 (0.12-0.63)	0.37 (0.16-0.87)	0.36 (0.15-0.87)
<209 (n = 206)	17 (18.2)	1.00	1.00	1.00
Climbing, Kcal/wk				
>175 (n = 250)	6			
57-175 (n = 233)	8 (2.9)	0.76 (0.35-1.68)	0.93 (0.41-2.07)	0.82 (0.37-1.80)
<57 (n = 266)	13 (4.9)	1.00	1.00	1.00
Moderate activity, Kcal/wk				
>6,749 (n = 250)	5			
3,455-6,749 (n = 246)	6 (2.2)	0.29 (0.12-0.66)	0.41 (0.17-0.98)	0.39 (0.17-0.91)
<3,455 (n = 253)	16 (6.3)	1.00	1.00	1.00
Vigorous activity, Kcal/wk				
Yes (n = 86)	1 (1.1)	0.36 (0.05-2.73)	0.40 (0.05-3.17)	0.46 (0.06-3.55)
No (n = 663)	26 (3.9)	1.00	1.00	1.00
Total, Kcal/wk				
>8,090 (n = 250)	5			
4,774-8,090 (n = 249)	4 (1.8)	0.24 (0.11-0.56)	0.38 (0.14-0.81)	0.34 (0.14-0.82)
<4,774 (n = 250)	18 (7.2)	1.00	1.00	1.00
CDCP/ACSM†				
Adhering (n = 459)	10 (2.2)	0.39 (0.17-0.91)	0.51 (0.23-1.19)	0.53 (0.23-1.23)
Not adhering (n = 290)	17 (5.9)	1.00	1.00	1.00

Values are hazard ratio (95% CI). Model 1 is adjusted for age, gender, education, and APOE genotype.Model 2 is adjusted as Model 1 + cardiovascular disease, hypertension, and hyperhomocysteinemia. Model 3 is adjusted as Model 1 + comorbidity and basic activities of daily living motor disability.

*Except when otherwise indicated, HRs for vascular dementia refer to the highest and middle tertiles pooled together compared to the lowest tertile.

†Centers for Disease Control and Prevention and the American College of Sports Medicine, recommendations for physical activity (see text).[21]

exclude that this is due to the small number of APOE ε4 carriers.

The strengths of this study are the population-based cohort, the longitudinal design, the ability to adjust for a large number of potential confounders, the estimation of energy expenditure for a large variety of physical activities, and the possibility of performing separate analyses for physical activities of different intensity.

The study has also several limitations. First, the study design cannot establish causal relationships and a 4-year follow-up is too short an interval to completely rule out the possibility that lower physical activity was not a cause but an early symptom of dementia. This possibility was addressed by using an extensive evaluation process in order to exclude from the investigation participants with prevalent and preclinical dementia. However, the presence of undetected cognitive impairment cases among the participants negative at cognitive screening cannot be excluded. Moreover, the international criteria for MCI used in this study, although designed to include non-AD dementia prodromal syndromes,[32] fail to provide specific criteria for a reliable identification of vascular MCI as opposed to the AD-prodromal type. This may have resulted in a selection bias of the study cohort and an artificial strengthening of the association between physical activity and VaD risk. Second, engaging in regular physical activity might not play a protective effect per se on cognitive function but only represent a marker of good overall health. To investigate this issue, we added to our models several variables related to baseline functional and health status and found that risk estimates remained unaffected. The small number of incident dementia cases and the wide CIs represent a third limitation. However, results for the VaD subtype reached a fair significance and were strongly consistent. Fourth, measures of physical activity are based on self-report. Fifth, except for one dementia case with MRI documentation, neuroimaging information was obtained from CT, which is inferior to MRI in detecting vascular lesions. Finally, the poor educational background and rural upbringing that characterize this cohort may make our results not applicable to other populations.

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論文名	Physical activity and dementia risk in the elderly: findings from a prospective Italian study						
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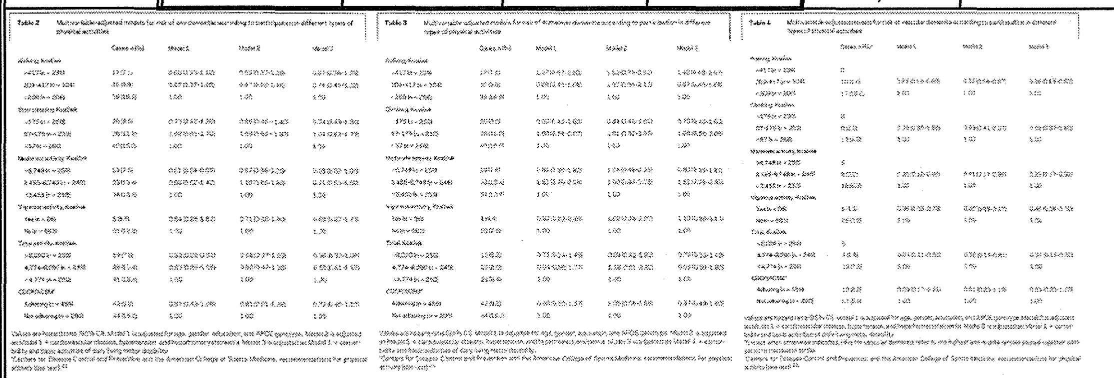
対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	73.2(±6.0)			( )		前向き研究
	対象数	500〜1000			( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	な し	な し	介護予防	認知症	( )
	維持・改善	な し	な し	な し	な し	( )	( )
図 表							
図表掲載箇所	P1790, Table2, P1791, Table3, P1792, Table4						
概 要 (800字まで)	本研究は、イタリアのThe Conselice Study of Brain Ageing(CSBA)に参加した男女749名を対象に、平均3.9年間の追跡調査を行い、身体活動量と認知症発症との関連を検討したものである。質問紙によって、次の3つの項目における身体活動量を尋ねた。1)1日当たりの運動目的または通勤時などの歩行距離、2)1日当たりに階段を昇降する回数、3)過去1年間において、週当たりの職業活動、余暇時間活動、スポーツを実施した期間と頻度。すべての活動をメッツ値に換算し、実施した身体活動量の合計を週当たりの消費カロリー(kcal/週)として表わした。週当たりの身体活動量が4,774kcal/週未満、4,774-8,090kcal/週、8.090kcal/週以上の3群に分類した。全認知症発症リスクおよびアルツハイマー病発症リスクにおいては、総身体活動量、中強度身体活動量、高強度身体活動量によるリスクの差異はみられなかったが、脳血管性認知症発症リスクについては、総身体活動量が4,774kcal/週以上で0.34(95%信頼区間:0.14-0.82)と有意なリスク減少がみられた。また、中強度身体活動量が3,455kcal/週未満の集団と比較すると、3,455kcal/週以上で0.39(0.17-0.91)の有意なリスク減少がみられた。						
結 論 (200字まで)	本研究における高齢コホートにおいては、身体活動量と脳血管性認知症発症リスクに負の相関が明らかとなったが、全ての認知症発症やアルツハイマー病発症リスクについては、同様の関連はみられなかった。						
エキスパートによるコメント (200字まで)	身体活動基準の策定に使用された研究である。認知症発症リスクと身体活動との関係を検討した点、脳血管性認知症だけが身体活動と関係する点を明らかにした点に意義がある。認知症の身体活動による予防効果の詳細を一層研究する必要がある。						

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Effect of Walking Distance on 8-Year Incident Depressive Symptoms in Elderly Men with and without Chronic Disease: The Honolulu-Asia Aging Study

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OBJECTIVES: To determine the effect of walking on incident depressive symptoms in elderly Japanese-American men with and without chronic disease.

DESIGN: Prospective cohort study.

SETTING: The Honolulu-Asia Aging Study.

PARTICIPANTS: Japanese-American men aged 71 to 93 at baseline.

MEASUREMENTS: Physical activity was assessed according to self-reported distance walked per day. Depressive symptoms were measured using an 11-question version of the Centers for Epidemiologic Studies Depression Scale (CES-D 11) at the fourth examination (n = 3,196) and at the seventh examination 8 years later (1999/00, n = 1,417). Presence of incident depressive symptoms was defined as a CES-D 11 score of 9 or greater or taking antidepressants at Examination 7. Subjects with prevalent depressive symptoms at baseline were excluded.

RESULTS: Age-adjusted 8-year incident depressive symptoms were 13.6%, 7.6%, and 8.5% for low (<0.25 miles/day), intermediate (0.25–1.5 miles/day), and high (>1.5 miles/day) walking groups at baseline (P = 0.008). Multiple logistic regression analyses, adjusted for age, education, marital status, cardiovascular risk factors, prevalent diseases, and functional impairment, showed that those in the intermediate and highest walking groups had significantly lower odds of developing 8-year incident depressive symptoms (odds ratio (OR) = 0.52, 95% confidence interval (CI) = 0.32–0.83, *P* = .006 and OR = 0.61, 95% CI = 0.39–0.97, *P* = .04, respectively). Analysis found that this association was significant only in participants without chronic diseases (coronary heart disease, cerebrovascular accident, cancer, Parkinson's disease, dementia, or cognitive impairment) at baseline.

CONCLUSION: Daily physical activity (≥0.25 mile/day) is significantly associated with lower risk of 8-year incident depressive symptoms in elderly Japanese-American men without chronic disease at baseline. **J Am Geriatr Soc 58:1447–1452, 2010.**

Key words: physical activity; aged; depressive symptoms; chronic disease

Depressive symptoms are common in older individuals and have been identified in 8% to 20% of older community-dwelling residents and up to 35% of older primary care patients.[1,2] Depression has been associated with greater morbidity and mortality and greater risk of physical decline and onset of disability.[3–6] Depression worsens many medical conditions, and some consider it to be a risk factor for the development of cardiovascular disease.[7] The World Health Organization has highlighted the detrimental effects of depression on medical illnesses as one of its 10 most-important global public statistics for 2007.[8]

The benefits of physical activity have been well documented in the literature, including for older individuals. It has been shown to improve aerobic capacity, coordination, and flexibility.[9] It decreases the risk of chronic disease comorbidity, slows the progression of disability, and has been associated with lower cardiovascular and all-cause mortality.[10,11] In addition, walking has been shown to improve mortality in nonsmoking retired men.[12]

Cross-sectional and longitudinal studies have shown the beneficial effects of physical activity on depressive symptoms in older cohorts.[13,14] Clinical trials have shown that exercise interventions result in sustained reductions in depressive symptoms for up to 5 years of follow-up,[15]

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although it is not clear whether physical activity has a protective effect on the development of new depressive symptoms. To study this question, data from elderly Japanese-American men in Hawaii were used to examine the cross-sectional and longitudinal relationships between walking distance and incident depressive symptoms. It was hypothesized that those who walked more would be protected against development of incident depressive symptoms, after adjustment for confounders.

METHODS

Study Design and Population

The Honolulu Heart Program (HHP) began in 1965 as a prospective population-based study of cardiovascular disease in 8,006 men of Japanese ancestry living on the island of Oahu, Hawaii. The men were born between 1900 and 1919. All men of Japanese ancestry identified by using World War II selective service registration cards were invited to participate. HHP cohort recruitment, design, and procedures have been described previously.[16] An expansion of the HHP was launched with the fourth examination in 1991 to 1993 as the Honolulu-Asia Aging Study (HAAS) to evaluate dementia, depression, and other diseases of aging.

The findings for this report are based on two time periods of data collection. The baseline for analysis was the fourth HHP-HAAS examination, which was conducted from 1991 to 1993 and included 3,741 men aged 71 to 93. The seventh examination was conducted from 1999 to 2000 and included 1,518 men aged 79 to 100. One thousand four hundred forty men died between the two examination periods, 775 who did not respond and eight who could not be located. For this report, walking distance as measured at the baseline examination (1991–1993) was used to predict incident depressive symptoms observed at the seventh examination (1999–2000).

Data Collection

Walking Distance

During the fourth examination (1991–1993), the subjects were asked how many city blocks they walked each day. Blocks were then converted into miles using 12 blocks per mile as a conversion factor. This assessment of physical activity was developed from the Harvard Alumni Survey, and validity and reliability have been determined previously.[17,18]

Depressive Symptoms

Participants were screened for depressive symptoms using an 11-question version of the Centers for Epidemiologic Studies Depression Scale (CES-D 11) (Appendix 1). Participants who did not answer three or more of the 11 depression questions were excluded from this analysis, leaving 3,196 participants with a valid CES-D 11 at Examination 4 (baseline). The standard 20-question CES-D uses a cutoff score of 16 points for depressive symptoms.[19] In the CES-D 11, a score of 9 or greater was used as a cutpoint (determined by extrapolation; $16/20 \times 11 = 8.8$, rounded up to 9). Shortened forms of the CES-D have been found to be comparable with the full-scale version.[20,21] Prevalent depressive symptoms were defined as a valid CES-D 11 score of 9 or greater or taking antidepressant medications at Examination 4 (338/3,196, 10.6%).

The CES-D 11 screening test was repeated during the seventh examination 8 years later, and again, subjects who did not answer three or more of the questions were excluded from the analysis. Subjects were defined as having 8-year incident depressive symptoms if they had a CES-D 11 score of 9 or greater or were taking antidepressant medications at Examination 7. Subjects with prevalent depressive symptoms at Examination 4 were excluded from the incidence analysis. Incident depressive symptoms were found in 126 of 1,282 men (9.8%).

Covariates

Baseline covariates were selected because of their potential relationships with depressive symptoms or physical activity. Education was determined according to self-report as number of years of formal education. Marital status was determined according to self-report (yes/no). Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher or when a study participant was receiving medications for the treatment of hypertension. Diabetes mellitus was defined according to the modified American Diabetes Association criteria, as fasting glucose of 126 mg/dL or greater, 2-hour postload glucose of 200 mg/dL or greater, or taking medication (insulin or oral hypoglycemics).[22] Alcohol use was determined according to self-report as ounces consumed per week. Smoking status was determined according to self-report, and subjects were classified as ever or never smokers. Prevalent coronary heart disease, stroke, and cancer were determined using hospital surveillance, with a physician panel making a final diagnosis by consensus using standardized research criteria. Cognitive function was measured using the Cognitive Abilities Screening Instrument,[23] which was developed for cross-cultural and cross-national studies of dementia. Cognitive impairment was defined as a score of less than 74 on the Cognitive Abilities Screening Instrument. This cut-point has a sensitivity of 80% and specificity of 90% for a diagnosis of dementia using *Diagnostic and Statistical Manual of Mental Disorders* (DSM), *Third Edition, Revised* criteria. An expert physician panel determined prevalent dementia and Parkinson's disease using standardized research criteria. Functional impairment was defined as self-reported difficulty walking half a mile.

Statistical Analysis

Subjects were divided into tertiles based on walking distance (low <0.25 miles/day, intermediate 0.25–1.5 miles/day, high ≥ 1.5 miles/day). To determine statistically significant differences between groups, chi-square tests were used to compare categorical variables, and t-tests or general linear models were used to compare continuous variables.

Multiple logistic regression models were used to estimate the odds of having incident depressive symptoms in the intermediate- and high-walking-distance groups, using the low-walking-distance group as reference. Adjustments were made for age, education, marital status, BMI, hypertension, diabetes mellitus, alcohol consumption, smoking status, prevalent coronary heart disease, stroke, cancer, Parkinson's disease, dementia or cognitive impairment, and functional impairment. Analyses also modeled distance walked as a continuous variable.

Because chronic diseases may affect physical activity, analyses were also stratified according to health status. Participants were defined as sick if they had prevalent coronary heart disease, stroke, cancer, Parkinson's disease, or dementia or cognitive impairment at baseline and healthy if no chronic medical disease was present at baseline. Adjustments were made for baseline age, education, marital status, cardiovascular risk factors, and functional impairment.

RESULTS

Means of baseline demographic factors, cardiovascular risk factors, and other comorbid prevalent conditions were compared according to walking groups. On average, men who reported walking longer distances were younger than those who reported walking less ($P<.001$). After adjusting for age, men who walked longer distances were significantly more educated; had lower alcohol consumption; were less likely to be ever smokers; and had lower rates of prevalent stroke, dementia or cognitive impairment, and functional impairment. Men who walked longer distances also had significantly lower rates of prevalent and 8-year incident depressive symptoms (Table 1).

Additionally, means of baseline demographic factors, cardiovascular risk factors, and other comorbid prevalent conditions were compared according to prevalent depressive symptoms. Participants who had depressive symptoms at baseline were significantly less likely to be married and to have lower BMI; a lower rate of hypertension; and higher rates of prevalent stroke, Parkinson's disease, dementia, cognitive impairment, and functional impairment (Table 2).

Logistic regression models were used to compare the odds of 8-year incident depressive symptoms separately in the intermediate- and high-walking-distance groups, using the low-walking-distance group as reference. Logistic regression models were unadjusted and were adjusted for several potential confounders. After adjusting for age, education, marital status, cardiovascular risk factors, prevalent diseases, and functional impairment, multivariate models found significantly lower odds of development of 8-year incident depressive symptoms in the high- (odds ratio (OR) = 0.61, 95% confidence interval (CI) = 0.38–0.97, $P=.04$) and intermediate-walking-distance (OR = 0.52, 95% CI = 0.32–0.84, $P=.007$) groups (Table 3). Subjects with prevalent depressive symptoms at baseline were removed from analyses of incidence.

Another logistic regression model was used to compare the odds of incident depressive symptoms in the intermediate- and high-walking-distance groups stratified for presence or absence of chronic diseases (sick vs healthy), again using the low-walking-distance group as reference. In multivariate models, adjusting for age, education, marital status, cardiovascular risk factors, and functional impairment, those in the intermediate-walking-distance group who were healthy had significantly lower odds of developing incident depressive symptoms (OR = 0.39, 95% CI = 0.21–0.71, $P=.002$). There was a trend toward significance in the odds of developing incident depressive symptoms in the high-walking-distance group (OR = 0.61, 95% CI = 0.35–1.06, $P=.08$). There were no significant associations between walking groups and depressive symptoms in the sick group for the intermediate- or high-walking-distance groups (Table 4).

DISCUSSION

This study investigated the association between self-reported walking distance and prevalent and 8-year incident depressive symptoms in a cohort of elderly Japanese-American men from the HHP and HAAS longitudinal cohort. As

Table 1. Baseline Characteristics According to Distance Walked per Day

	Distance Walked, Miles/Day			
Characteristic	<0.25 (n = 1,090)	0.25–1.5 (n = 1,160)	>1.5 (n = 946)	*P*-Value
Age, mean	77.8	77.5	76.4	<.001
Education, years, mean	10.4	10.8	10.9	.002
Married, %	83.0	83.1	83.1	.95
Body mass index, kg/m^2, mean	23.5	23.6	23.6	.28
Hypertension, %	73.1	75.3	75.8	.17
Diabetes mellitus, %	31.3	30.0	27.8	.09
Alcohol, oz/day	20.5	18.7	15.2	.003
Ever smoker, %	65.1	62.0	59.8	.01
Prevalent coronary heart disease, %	22.0	20.8	23.5	.41
Prevalent cerebrovascular attack, %	5.5	4.0	3.2	.009
Prevalent cancer, %	13.6	13.8	12.6	.53
Prevalent Parkinson's disease, %	1.3	0.5	0.8	.25
Prevalent dementia or cognitive impairment, %	13.7	8.8	7.6	<.001
Prevalent functional impairment, %	23.7	13.7	4.3	<.001
Prevalent depressive symptoms, %	12.2	11.2	7.9	.005
8-year incident depressive symptoms, %	13.6	7.6	8.5	.008

All characteristics except age adjusted for age.