ORIGINAL CONTRIBUTION

Risk of Amyotrophic Lateral Sclerosis and History of Physical Activity

A Population-Based Case-Control Study

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Objective: To assess in greater detail than previous studies the purported association between a history of physical activity and amyotrophic lateral sclerosis (ALS).

Methods: A population-based case-control study was used to identify risk factors for ALS. Case patients were from 3 counties of western Washington State who were newly diagnosed as having ALS by a neurologist. Two control subjects matched with each case patient for sex and age within 5 years were identified by random digit telephone dialing or random selection from Medicare eligibility lists. All subjects underwent an in-person structured interview including detailed information about physical activity be-- fore a reference date, which was the month and year the case patient was diagnosed as having ALS. Various measures of physical activity both at work and leisure time were evaluated using conditional logistic regression taking into account the matching for sex and age.

Results: One hundred seventy-four case patients and 348 control subjects participated in the study. Physical activity was not significantly different between case patients and controls—whether at work, leisure time or both combined, and whether during a person's lifetime (from 10 years before reference date back to age 15 years) or during specific decades before reference date. An exception was that case patients reported having participated in organized sports in high school slightly more frequently than control subjects (odds ratio, 1.52; 95% confidence interval, 1.03-2.25).

Conclusion: A history of physical activity has little, if any, effect on the risk of ALS.

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AMYOTROPHIC LATERAL sclerosis (ALS) is a devastating disease for which a satisfactory treatment is lacking. Some interplay among immutable host factors and modifiable environmental and behavioral factors likely determines who will develop ALS. Identification of causative risk factors could provide clues about its pathophysiological features and prevention. Several epidemiological studies of ALS have suggested that vigorous physical activity, both at the workplace and during leisure time, may be such a risk factor[1,2] although a recent case-control study did not.[3]

The idea that physical activity could be related to ALS is not a new one. During a conference on ALS in 1962, Critchley commented:

> Nothing has been said about the possible role in aetiology of a previous habit of athleticism. I have the uncomfortable feeling that a past history of unnecessary muscular movement carried out for no obvious reason may be followed in later life by the development of motor neurone disease in a statistically significant number of cases.[4]

Well-publicized instances of ALS in professional athletes—such as baseball's Lou Gehrig, football's Matt Hazeltine, and boxing's Ezzard Charles—likely contributed to the concept of vigorous physical activity as a risk factor. Physical activity could affect the risk of ALS because exposure to a neurotoxin selective for motor neurons occurred at the time of exercise or because exercise modified the effects of a neurotoxin.[2] To identify causative risk factors for ALS, we performed a population-based case-control study and examined in detail physical activity before the diagnosis of ALS.

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PATIENTS AND METHODS

During 4 years beginning in 1990, we identified all incident cases of ALS occurring in residents of King, Pierce, and Snohomish Counties of western Washington State.[5,6] These are the most populous counties in the state, having about 2.5 million people in 5900 square miles. To be eligible for the study, patients had to be residents of 1 of these 3 counties, aged 18 years or older, and diagnosed as having ALS by a neurologist. Patients had to have progressive motor neuron disease that affected both upper and lower motor neurons or lower motor neurons alone. Patients were excluded if they had primary lateral sclerosis or if a diagnosis other than ALS became apparent during the year after their initial diagnosis.

Two control subjects, matched to each case patient for sex and age within 5 years, were identified from the target counties using 1 of 2 techniques. The first was random digit telephone dialing using the Mitofsky-Waksberg sampling protocol.[7,8] More than 97% of the region's households had telephones based on the 1990 census.[9] Because random digit dialing proved to be inefficient for identifying control subjects 65 years or older, partway through the study we adopted an alternative technique using Medicare eligibility lists, obtained from the Health Care Finance Administration. Potential control subjects matched for sex and age were randomly selected from the list for the target counties and sent a letter explaining the study and requesting their participation.

Information about demographics and past exposures, including physical activity, was collected during a structured in-person interview. Some of the questions were linked to a reference time. For the case patients, this time was the month and year of their ALS diagnosis, which qualified them for the study. For the control subjects, this time was the same as for their matched case patient.

Detailed information was collected on physical activity, for both workplace and leisure time, from the reference date back to age 15 years old. A personalized calendar was used to record major life events to assist recall. For workplace physical activity, subjects detailed all jobs that they had held for 1 year or longer starting with the reference date and going back in time. Subjects indicated the year when they started and ended a job and the average number of hours worked per week. For each job, subjects estimated the percentage of time spent in each of 5 levels of physical activity: (1) sedentary activities, such as sitting, standing, or driving; (2) walking; (3) doing light physical work that did not cause sweating, such as pushing or pulling light objects or reaching to stock shelves; (4) doing moderate physical work that caused heavy breathing or sweating, such as lifting or carrying less than 11.2 kg; and (5) doing heavy physical work that caused heavy breathing or sweating, such as lifting or carrying more than 11.2 kg.

For each year from the reference date back to age 15 years, we calculated the number of hours spent at each level of workplace physical activity. An annual index of all levels of workplace physical activity was computed by summing the hours per year spent at each activity level multiplied by an intensity weighting for each level. The lifetime index took the average of the annual indexes for all the years from 10 years before the reference date to age 15 years. Using the reports of control subjects, we created tertiles of these lifetime indexes. In addition, we defined levels 4 and 5 as vigorous physical activity in the workplace. The lifetime hours of vigorous physical activity was the average of the number of hours per year spent in vigorous physical activity for all the years from 10 years before the reference date to age 15 years. Using information from control subjects to estimate the median number of hours of vigorous physical activity in the workplace, we defined 3 groups: those without vigorous physical activity; those with low levels (less than the median number of hours per year among those reporting some vigorous physical activity); and those with high levels (the median number of hours per year or more).

RESULTS

During the 4 years of the study, 180 patients newly diagnosed as having ALS met the study criteria, and 174 (97%) agreed to participate. Only 4 (2%) of those interviewed indicated that they had a first-degree relative also affected by ALS, and only 1 of these 4 had more than a single affected relative. Using random digit dialing, 4858 residential telephone numbers were reached. People at 4209 (87%) of these households allowed a screening interview to establish if an eligible subject was in the household. All 262 eligible subjects were invited to participate, and 227 (87%) agreed to participate in the study. The overall response rate was 75%. Of the potentially eligible control subjects identified through random selection from Medicare eligibility lists, 121 (60%) of 202 agreed to participate. Twenty case patients died before the interview. For each dead case patient and corresponding control subjects, information was obtained from a surrogate.

The case patients and control subjects were the same for sex and were similar for age, racial groups, and marital status (**Table 1**). Case patients had less formal education than control subjects. Because of the potential for confounding by education, it was included, along with age, in all subsequent models.

Physical activity in the workplace was not associated with case-control status whether considering the tertiles of lifetime index of any physical activity from 10 years before the reference date to age 15 years or the 3 levels of hours spent in vigorous physical activity over the same time (**Table 2**). Similarly, using a sliding 10-year window going back in time from the reference date, no period of significantly increased or decreased risk was identified for low or high levels compared with no vigorous physical activity in the workplace (**Figure 1**).

Similar negative results were found for leisure time physical activity (Table 2 and **Figure 2**) and for the location of the leisure time physical activity, whether indoors or outdoors (Table 2). None of the particular leisure time physical activities was significantly associated with case-control status. For example, the 10 most frequently performed activities are listed in **Table 3**. Participation in amateur or professional sports and the use of anabolic steroids, dimethyl sulfoxide, or liniments were not related to case-control status (Table 2). Case patients were slightly, but significantly, more likely to have

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Subjects also provided detailed information on all leisure time physical activities in which they engaged at least twice per month from the reference date back to age 15 years. Subjects indicated at what age they began and ended the activity, and how much time was spent performing the activity. Using a compendium of physical activities,[10] we assigned a value to each activity that reflects the estimated rate of energy expenditure for that activity. The value is defined as the ratio of the metabolic rate for the particular activity relative to the resting metabolic rate, so-called MET values. As with physical activity in the workplace, we computed an annual index of all leisure time physical activity by summing the hours per year spent at each activity multiplied by the activity's MET value. The lifetime index took the average of the annual indexes for all the years from 10 years before the reference date to age 15 years. Again, using the reports of control subjects, we created tertiles of these lifetime indexes. We also defined vigorous physical activities as those with MET values of 6 or more. Examples of such activities include playing handball, home exercises, and mowing the lawn with a push mower. The average number of hours per year spent in vigorous physical activity was considered as a 3-level variable with no, low, or high levels. The risk of ever having engaged in specific leisure time physical activities was also examined.

In addition, we classified each leisure time physical activity as taking place predominantly indoors, outdoors on playing fields, or outdoors not on playing fields. Three-level variables were computed as described above. Specific questions were asked about participation in organized sports during high school and at other times; employment as a professional or semiprofessional athlete; and use of anabolic steroids, dimethyl sulfoxide, and other liniments.

Finally, as an overall summary, subjects were asked to estimate for each decade beginning at age 15 years and going up to the reference date the average number of times per year that they engaged in physical activities that were demanding enough to cause them to breathe heavily or to sweat either on or off the job. Questions were also asked about hours spent in household physical activities, such as with household chores or active child care. For these questions, the average number of times or of hours per year were examined as the 3-level variable as defined above.

Associations between ALS and potential risk factors were assessed using conditional logistic regression.[11] Case patients were paired with the 2 unique control subjects who were matched for age, sex, and respondent type. Odds ratios (ORs) and their 95% confidence intervals (CIs) were derived from these analyses. An OR is considered statistically significant if its 95% CI does not include 1. Given the possibility of residual confounding by age, it was included in every model as a continuous variable. Some analyses included the time period from 10 years before reference date to age 15 years. Ten years was chosen to exclude the potential effects of subclinical disease before the reference date, the date of a case patient's diagnosis. When examining variables with 3 levels, the level with the least physical activity was used as the reference. Other analyses examined exposures in a 10-year window starting with the reference date and going back in time to investigate the possibility of a latent period. Odds ratios and their 95% CIs were derived and then the 10-year window was slid back 1 year at a time. A curve was constructed that summarized all these ORs and their 95% CIs. This approach, using a sliding 10-year window, is akin to a moving average and ensures that periods in the past during which the risk may have been increased or decreased would not be missed by considering a more extended period of time. The Human Subjects Committee at the University of Washington, Seattle, approved the study.

participated in organized sports during high school than control subjects (OR, 1.52; 95% CI, 1.03-2.25).

The sliding window analyses were repeated for indoor and outdoor activities and still failed to show any patterns of increased or decreased risks. Similarly, sliding window analyses examining age of the subject and calendar year instead of time since the reference date were negative (data not shown).

Risks for overall times of vigorous physical activity in and out of the workplace and hours of household physical activities per year for decades from age 15 years to the reference date are displayed in **Figure 3** and **Figure 4**. A trend for increased risk at younger ages was present for high levels of vigorous physical activity, but not for the low levels and not for household physical activities. This trend had been statistically significant in preliminary analyses that included 104 case patients,[12] but the significance was lost when the full data set was analyzed.

Table 1. Demographic Information on Case Patients and Control Subjects Matched for Sex and Age Within 5 Years

Characteristic	No. (%) Case Patients (n=174)	No. (%) Control Subjects (n=348)
Sex		
M	95 (54.6)	190 (54.6)
F	79 (45.4)	158 (45.4)
Age group, y		
18-44	22 (12.6)	46 (13.2)
45-54	28 (16.1)	67 (19.3)
55-64	49 (28.2)	75 (21.5)
65-74	52 (29.9)	114 (32.8)
≥75	23 (13.2)	46 (13.2)
Racial group		
White	163 (93.7)	329 (94.5)
Other	11 (6.3)	19 (5.5)
Marital status		
Single	8 (4.6)	12 (3.5)
Married	119 (68.4)	242 (69.5)
Other	47 (27.0)	94 (27.0)
Education status		
≤High school	83 (47.7)	124 (35.6)
>High school	91 (52.3)	224 (64.4)

COMMENT

Despite the suggestion from previous studies[1,2] of an association between ALS and physical activity and

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Table 2. Summary of Analyses Examining Association Between Physical Activity and Amyotrophic Lateral Sclerosis

Physical Activity Measure*	Case Patients, % (n=174)	Control Subjects, % (n=348)	Model† OR	Model† 95% CI
Workplace				
Lifetime index of any physical activity				
First tertile	33.1	33.3	1.00	. . .
Second tertile	30.2	33.3	0.96	0.58-1.61
Third tertile	36.7	33.4	1.07	0.57-2.03
Lifetime vigorous physical activity				
None	27.8	35.9	1.00	. . .
Low level	38.5	31.9	1.61	0.98-2.65
High level	33.7	32.2	1.28	0.74-2.21
Leisure time				
Lifetime index of any physical activity				
First tertile	27.9	33.2	1.0	. . .
Second tertile	33.1	33.2	1.17	0.73-1.87
Third tertile	39.0	33.6	1.46	0.89-2.39
Lifetime vigorous physical activity				
None	13.4	12.1	1.00	. . .
Low level	40.7	43.9	0.96	0.52-1.76
High level	45.9	44.0	1.20	0.64-2.23
Indoor vigorous physical activity				
None	14.5	14.1	1.00	. . .
Low level	35.5	43.1	0.90	0.50-1.60
High level	50.0	42.8	1.24	0.71-2.19
Outdoor vigorous physical activity on playing field				
None	10.5	10.4	1.00	. . .
Low level	50.0	44.8	1.10	0.56-2.17
High level	39.5	44.8	0.91	0.46-1.82
Outdoor vigorous physical activity not on playing field				
None	8.7	8.8	1.00	. . .
Low level	49.4	45.7	1.17	0.59-2.32
High level	41.9	45.5	0.98	0.49-1.98
Participation in organized sports during high school	45.7	37.6	1.52	1.03-2.25
Participation as an amateur competitive athlete, other than during schooling	11.5	8.6	1.45	0.78-2.69
Ever employed as a professional athlete	0.6	1.2	0.43	0.04-4.56
Ever use anabolic steroids	0.6	0	. . .	. . .
Ever use dimethyl sulfoxide	4.6	4.0	1.22	0.49-3.03
Ever use other liniments	16.3	18.7	0.80	0.48-1.33

*See "Methods" section for details about how measures were defined. Concerning measures of workplace physical activity, information was missing for 5 case patients but no control subjects, and concerning leisure time for 2 case patients and 2 control subjects. Ellipses indicate not applicable.

†Odds ratios (ORs) and 95% confidence intervals (CIs) derived from conditional logistic regression taking into account matching for sex and age within 5 years. Each model also contained age as a continuous variable and education. When 3 groups were compared, the one with the least physical activity was used as the reference group and assigned an OR of 1.00.

results from preliminary analyses of this study,[12] we found essentially no such association in the final analyses of this study, either for overall or vigorous physical activity, either workplace or leisure time. A recent case-control study[3] came to a similar conclusion. In the current study, we were able to avoid some of the problems that have marred previous studies.[1,2] We used a population-based case-control design, with a relatively large number of incident cases, and with detailed information on lifetime physical activity. Case patients and control subjects differed with respect to

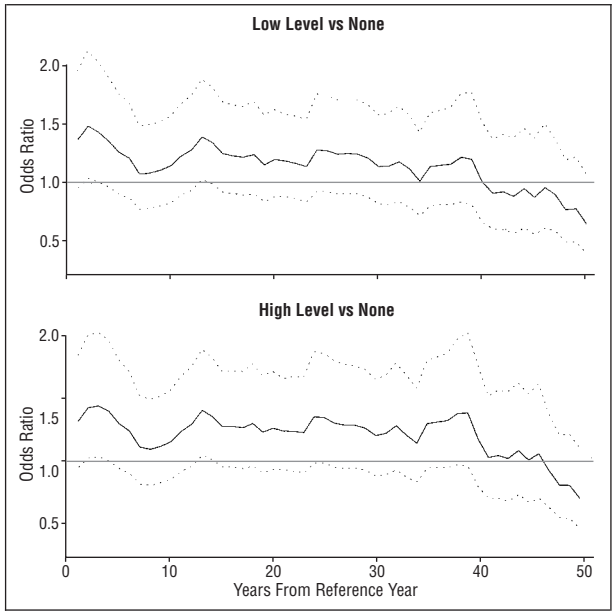

Figure 1. *Odds ratios (solid lines) and 95% confidence intervals (dotted lines) for the risk of amyotrophic lateral sclerosis with low levels and high levels compared with no vigorous physical activity in the workplace. Each point represents the odds ratio derived from a conditional logistic regression model for the 10 years immediately before the time indicated by the point. Each model took into account the matching for sex and age and included age and education. For the case patients and their matched control subjects, reference date was the month and year that the case patient was diagnosed as having amyotrophic lateral sclerosis.*

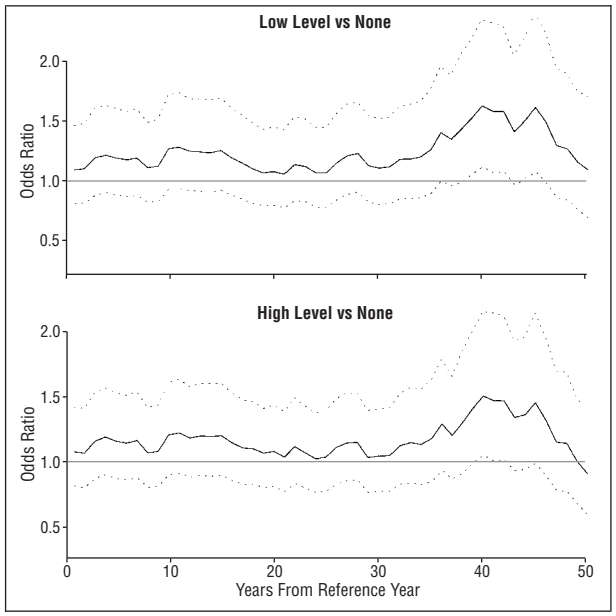

Figure 2. *Odds ratios (solid lines) and 95% confidence intervals (dotted lines) for the risk of amyotrophic lateral sclerosis with low levels and high levels compared with no vigorous physical activity during leisure time (see legend to Figure 1 for explanation as to what each point on the curve means).*

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Table 3. Summary of Association Between Specific Leisure Time Physical Activity and Amyotrophic Lateral Sclerosis

Physical Activity (Ever Performed)	Case Patients, % (n=174)	Control Subjects, % (n=348)	Model* OR	Model* 95% CI
Gardening: weeding, cultivating garden	61.5	64.7	0.89	0.60-1.32
Walking for pleasure (≥1.6 km)	57.5	58.0	1.05	0.71-1.55
Mowing lawn walking behind push mower	56.9	63.5	0.72	0.48-1.08
Dancing: ballroom and/or square	50.6	51.4	1.00	0.68-1.46
Bicycling for pleasure or to and from work	42.5	45.4	0.97	0.66-1.42
Bowling (1 game, 10 min)	42.0	39.9	1.04	0.71-1.53
Baseball, softball	36.8	36.2	1.05	0.71-1.55
Fishing from river bank or from a boat	35.1	33.6	0.98	0.64-1.49
Raking leaves	35.0	35.9	0.95	0.64-1.40
Home exercises	31.0	32.5	1.0	0.68-1.47

**Odds ratios (ORs) and 95% confidence intervals (CIs) derived from conditional logistic regression taking into account matching for sex and age within 5 years. Each model also contained age as a continuous variable and education.*

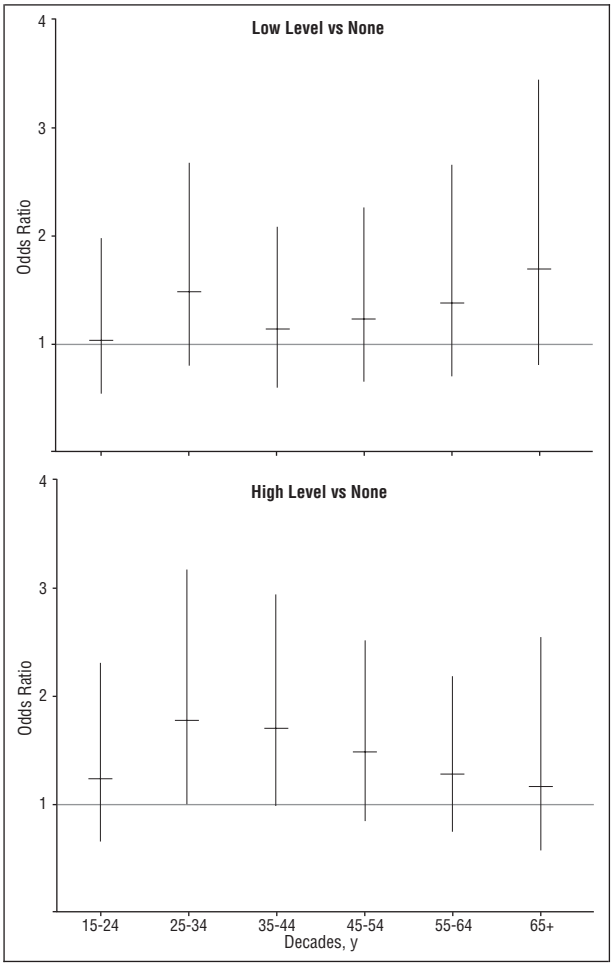

Figure 3. *Odds ratios (horizontal dashes) and 95% confidence intervals (vertical bars) for risk of amyotrophic lateral sclerosis with low and high levels of vigorous physical activity in or out of the workplace compared with none for specific decades beginning at age 15 years. Bars indicate upper or lower 95% confidence intervals.*

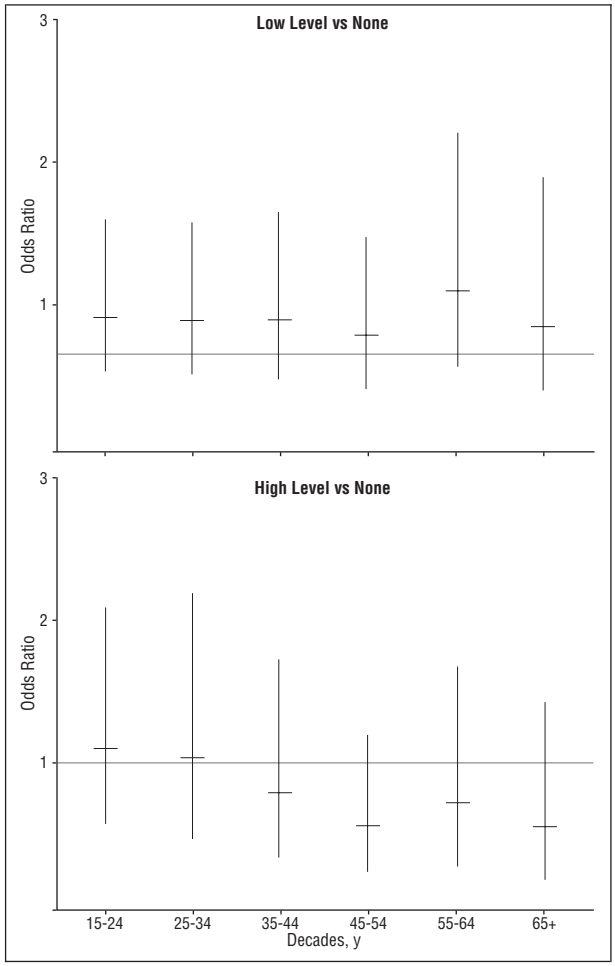

Figure 4. *Odds ratios (horizontal dashes) and 95% confidence intervals (vertical bars) for risk of amyotrophic lateral sclerosis with low and high levels of hours of household physical activities compared with none for specific decades beginning at age 15 years. Bars indicate upper or lower 95% confidence intervals.*

education, probably reflecting a greater willingness of potential control subjects with more education to participate in such studies than potential control subjects with less education. To adjust for this imbalance, education was included in all the multivariate models although it had little effect on the ORs.

Possibly, we were unable to detect an association because the effects of physical activity were small or because we failed to adjust for some other unrecognized confounding factor. Nonetheless, this study was larger than previous studies suggesting an association, and most of the current results did not even suggest a trend of in-

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creased risk with increased physical activity. The single exception was a slightly, but significantly, elevated risk with a report of participating in organized sports during high school (OR, 1.52; 95% CI, 1.03-2.25). Interestingly, a trend was present for an association between ALS and vigorous physical activity in and out of the workplace at a young age, but none of the ORs were statistically significant.

Not addressed in this report is the possible effect of either a history of physical activity or ongoing physical activity on the progression of ALS. Of interest, in a transgenic model of familial ALS, more physically active mice showed no difference in onset of clinical disease or in survival compared with more sedentary mice.[13]

In this study, we have confirmed the opinion expressed in the 1940 text by Wilson and Bruce[14]: "The view that strenuous occupations predispose must be received with caution; workmen, athletes and others engaged in heavy muscular performances are sometimes affected, but to a very large number more, the theory does not apply." Although physical activity seems unlikely to be an important risk factor for ALS, the search should continue for such factors because they may supply clues about the pathogenesis and prevention of the disease.

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