Abstract—Several famous athletes have been affected by ALS, and some epidemiologic studies have indicated that vigorous physical activity (heavy labor or athletics) is a risk factor for the disease. In a case-control study of 279 patients with motor neuron diseases and 152 with other neurologic diseases, the authors found that subjects with motor neuron diseases were more likely than controls to report they had always been slim or they had been varsity athletes. For slimness, the odds ratio (OR) was 2.21; 95% CI, 1.40 to 3.47. For varsity athletics, the OR was 1.70; CI, 1.04 to 2.76.

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Premorbid weight, body mass, and varsity athletics in ALS

Several celebrities with ALS were professional athletes—Lou Gehrig (baseball player), Ezzard Charles (heavyweight boxing champion), Catfish Hunter (baseball player), and football players among them. United States Senator Jacob Javits was an avid tennis player. David Niven was a competitive sailor. Dmitri Shostakovich and Charles Mingus played musical instruments vigorously. Was their athleticism simply a coincidence? In some previous studies, vigorous physical activity in the form of either heavy labor or competitive athletics was associated with ALS, although others found no such association.

We have also noticed that many patients with ALS seem to have had a lifelong lean habitus.

Subjects and methods. Subjects. The 431 subjects were consecutive patients seen between 1992 and 2000 in the practice of L.P.R. In a questionnaire, subjects were asked whether they had always been slim and whether they had been varsity athletes in high school, college, or thereafter. Responses to these questions were “yes” or “no.” The subjects also recorded their estimated premorbid height and weight, from which a premorbid body mass index (BMI) was calculated (the weight in kilograms divided by the square of height in meters). In previous studies, self-reports of weight and height (up to 28 years in the past) have been highly correlated with measured ones (r = 0.822). We excluded 11 possible controls with no clear past) have been highly correlated with measured ones (r = 0.822). We excluded 11 possible controls with no clear past) have been highly correlated with measured ones (r = 0.822). We excluded 11 possible controls with no clear past) have been highly correlated with measured ones (r = 0.822).

The subjects also recorded their estimated premorbid height and weight, from which a premorbid body mass index (BMI) was calculated (the weight in kilograms divided by the square of height in meters). In previous studies, self-reports of weight and height (up to 28 years in the past) have been highly correlated with measured ones (r = 0.822). We excluded 11 possible controls with no clear neurologic diagnosis and 25 subjects with age-related decline in athletic performance who had normal findings on neurologic examination.

For the classification of motor neuron disease we used four diagnostic categories (table 1). Application of the El Escorial diagnostic criteria did not alter the results. The control group comprised patients with other neurologic diseases (see table 1).

Statistical analyses. The data were analyzed in a retrospective case-control design. Logistic regression was used to calculate the OR of being diagnosed with motor neuron disease in association with the variables of interest. The National Heart, Lung, and Blood Institute guidelines were used to divide BMI into three categories.

Results. Patients with motor neuron disease were significantly more likely to have been slim and to have been varsity athletes (table 2). Patients and controls were similar in sex. Reported premorbid BMI was lower for subjects who reported they had always been slim (mean, 22.9; SD, 2.9) compared to subjects who did not (mean, 28.6; SD, 4.3; t = 14.97; p < 0.001). Reported premorbid BMI did not differ between athletes and nonathletes (t = 0.38; p < 0.70).

The odds of having motor neuron disease was 2.21 times higher in subjects who reported they had always been slim than in those who did not, and 1.70 times higher in subjects who reported they had been varsity athletes than in those who did not (see table 2). When premorbid BMI was used as a categorical variable there was a 2.48-fold increased risk for subjects whose premorbid BMI was in the normal/underweight range compared to those whose premorbid BMI was in the obese range (OR = 2.48). When premorbid BMI was used as a continuous variable we found a 6% increased risk for motor neuron disease for each unit decline of BMI (OR = 1.06, 95% CI; 1.01 to 1.11) (not recorded in table 2).

When we simultaneously introduced age at onset of symptoms, sex, BMI (as a categorical variable), slimness, and varsity athlete variables in a single logistic regression model, age at onset (OR, 1.05; 95% CI, 1.03 to 1.07), being always-slim (OR, 2.10; 95% CI, 1.08 to 4.07), and having been a varsity athlete (OR, 1.89; 95% CI, 1.05 to 3.40) were all associated with increased risk for motor neuron disease, but sex (OR, 0.91; 95% CI, 0.53 to 1.58) and BMI were not significant (probably because the BMI effect was carried by the highly correlated always slim variable).

To examine the association between ALS in particular rather than motor neuron disease in general (i.e., including purely lower or purely upper motor neuron syndromes) and variables of interest, we combined ALS and ALS-probable upper motor neuron signs into a single ALS diagnostic category (used as the dependent variable) and repeated all the regression analyses. The results were unchanged.

Discussion. Two previous studies failed to detect significant associations between premorbid body weight and motor neuron disease, but the results were significant here. The earlier studies may have been underpowered to detect a true difference. The

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always-slim status in motor neuron disease patients could imply more vigorous premorbid physical activities, which seemed to increase the likelihood of ALS in some epidemiologic studies: ALS patients were more likely to have engaged in heavy labor than controls.2 However, others found no association between occupation requiring physical exertion and motor neuron disease.

Reported associations between ALS and physical trauma or limb injury could have been related to vigorous physical activity that led to injury. As for athletics in ALS, the results have been inconsistent. In two studies, patients with ALS were more likely to have earned major athletic awards or varsity letters1 or to have participated in active sports than controls.2 However, others failed to demonstrate any association between athletics and ALS.2,4,5 The present series is the largest to address this question. All the previous negative studies may have been underpowered to detect a significant association because the number of subjects was insufficient, whereas the larger sample size in the present study sufficed.

Only 14% of US adults aged 18 to 29 years participate in physical activities [http://www.cdc.gov/nccdphp/sgr/summary.htm] that are much less intense than varsity training; even fewer qualify for varsity sports. The numbers of our motor neuron disease patients (38.2%) and controls (26.7%) were both higher than these population estimates.

Longstreth et al.8 summarized hypotheses that might explain the role of athletics. Vigorous physical activity might increase exposure to environmental toxins, facilitate the transport of toxins across the blood–brain barrier, increase the absorption of a toxin by the lower motor neurons, or increase susceptibility of motor neurons supplying fast-twitch fibers by stressing activity. For example, poliovirus seemed to affect limbs that had been exercised at the time of infection.9 Alternatively, being slim and athletic might be a phenotypic expression of genetic susceptibility to ALS, mediated by some environmental agent.

The case-control design of this study may place constraints on the validity of the exposure measurement and may blur the temporal relation between exposure and disease status. For example, in our study slimness could be an early manifestation of motor neuron disease rather than a risk factor. Also, obesity could be an early manifestation of the neurologic disease in the controls, who might have gravitated to a sedentary lifestyle before recognition of symptoms. However, these possibilities would not explain the difference in participation in varsity sports because, by definition, this occurred during high activity.

### Table 1 Frequencies and percentages of subjects in diagnostic groups of motor neuron disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequencies (% of all subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS with upper and lower motor neuron signs (ALS)</td>
<td>172 (40)</td>
</tr>
<tr>
<td>ALS with lower motor neuron signs and probable upper motor neuron signs</td>
<td>58 (14)</td>
</tr>
<tr>
<td>(active tendon reflexes in limbs with lower motor neuron signs but no clonus, Hoffmann signs, or Babinski signs) (ALS-PUMNS)</td>
<td></td>
</tr>
<tr>
<td>Progressive spinal muscular atrophy (lower motor neuron signs only) (PSMA)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Primary lateral sclerosis without lower motor neuron involvement (clinically or on electromyography) (PLS)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Controls* (other neurologic diseases)</td>
<td>152 (35)</td>
</tr>
</tbody>
</table>

* Diagnoses among 152 controls: peripheral neuropathies (16.1%); MG (10.3%); benign fasciculation (7%); muscular dystrophies (7%); inflammatory myopathies (6.5%); other myopathies (5.8%); movement disorders (4.5%); mitochondrial disorders (3.2%); cervical or lumbar spondylosis (3.2%); benign cramp syndromes (2.6%); MS (1.9%); and other conditions (13%, each less than 2%).

### Table 2 Subjects who reported always being slim; being varsity athletes; and in the three body mass index (BMI) categories in the motor neuron disease and control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Motor neuron disease, n (%)</th>
<th>Controls, n (%)</th>
<th>Simple model,* OR (95% CI)</th>
<th>Adjusted model,* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always slim</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79 (33.1)</td>
<td>61 (52.1)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>160 (66.9)</td>
<td>56 (47.9)</td>
<td>2.21 (1.40–3.47)</td>
<td>2.10 (1.08–4.07)</td>
</tr>
<tr>
<td>Varsity athlete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>144 (62.1)</td>
<td>89 (73.6)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>88 (37.9)</td>
<td>32 (26.4)</td>
<td>1.70 (1.04–2.76)</td>
<td>1.89 (1.05–3.40)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>27 (10)</td>
<td>29 (21)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Overweight (25–29.9)</td>
<td>95 (35)</td>
<td>46 (33)</td>
<td>2.22 (1.18–4.17)</td>
<td>1.41 (0.62–3.19)</td>
</tr>
<tr>
<td>Normal/underweight (≤24.9)</td>
<td>148 (55)</td>
<td>64 (46)</td>
<td>2.48 (1.36–4.53)</td>
<td>1.13 (0.44–2.89)</td>
</tr>
</tbody>
</table>

* The unadjusted (each variable included independently in each analysis) and adjusted odds ratios (OR) (age at symptom onset, sex, always-slim, varsity athlete, and BMI as a categorical variable simultaneously included in a single analysis) from logistic regression.
school or college, which was too long before symptom onset to be confused with disease manifestations. Elucidation of the pathophysiology that might account for these associations would require a prospective study recording the nature (athletic, heavy labor, isometric, aerobic, power, endurance), setting (indoors, outdoors, season), and intensity (frequency, level of competition, caloric expenditure, duration) of the physical activity, as well as environmental/occupational and toxin exposure data, including time between exposure and symptom onset.

Thousands and thousands of slim athletes never develop ALS. Why a tiny few of them do develop ALS is still unknown. There is certainly no justification to avoid athletics in attempts to avoid motor neuron diseases. Moreover, nothing in our data can be construed as evidence that patients with ALS should not exercise or that they should not be as well nourished as possible.

References

Abstract—Previous research suggests that response times for imagined movements provide a sensitive measure of the integrity of the motor system. In a group of 12 patients with chronic unilateral arm pain, the authors demonstrate that response times for imagined movements are influenced by the severity of pain. Simulated large-amplitude arm movements were slower for the painful as compared with the unaffected arms before, but not after, effective music therapy entrainment, suggesting that mental representations of movement are influenced by the current state of nociceptive feedback.

Pain and the body schema: Effects of pain severity on mental representations of movement

Several lines of evidence provide support for an online representation of the body in space (“body schema”) and its role in the guidance of imagined and actual movements.14 For example, Parsons argues that the body schema underlies performance on a task that requires participants to judge the laterality of pictured hands.1 Response times on this task suggest that participants confirm laterality judgments by imagining their hand moving from its current orientation into the orientation of the pictured hand; response times reflect the disparity between the orientations of stimulus and participant hands as well as biomechanical constraints on movement. For example, just as it takes longer to rotate a hand away from rather than toward the body midline, due to biomechanical constraints, laterality judgment times are longer when they involve imagining a hand rotating away as compared to toward the body midline. We have recently replicated the above findings and demonstrated that performance on the hand laterality task is sensitive to whether movements, if actually executed, would be painful.2 Patients with chronic unilateral arm pain exhibited significantly slower response times for the painful as compared with the normal arms in conditions that required large-amplitude imagined movements involving both
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