A recent meta-analysis of 7 genome-wide association studies on early balding (alopecia) revealed single nucleotide polymorphism variants in the region of the amyotrophic lateral sclerosis (ALS) gene TAR DNA-binding protein 43 (TARDBP/TDP-43). We therefore explored the association of early-onset alopecia and ALS in the Health Professionals Follow-up Study, a large cohort of 51,529 US men. In 1992, the participants (then aged 46–81 years) were asked to report their hair line pattern at age 45 years. During the follow-up period (1992–2008), 42 men were diagnosed with ALS. Of those, 13 had reported no alopecia, 18 had reported moderate alopecia, and 11 had reported extensive alopecia at age 45 years. Those who reported extensive alopecia had an almost 3-fold increased risk of ALS compared with those who reported no alopecia (relative risk = 2.74, 95% confidence interval: 1.23, 6.13). Furthermore, we observed a linear trend of increased risk of ALS with increasing level of balding at age 45 years ($P_{\text{trend}} = 0.02$). In conclusion, men with early-onset alopecia seem to have a higher risk of ALS. The mechanisms underlying this association deserve further investigation.
Alopecia and Amyotrophic Lateral Sclerosis

Person-time was calculated from the date of return of the 1992 questionnaire until the date of first onset of ALS symptoms (37 cases), death from ALS or any other cause (5 cases), or the end of follow-up (December 31, 2008). Cox proportional hazards regression was used to estimate relative risks and 95% confidence intervals for different stages of alopecia in relationship to ALS. We stratified the Cox models by age in single years to obtain better age adjustment.

There are few established risk factors for either alopecia or ALS. Smoking has been suggested to increase the risk of ALS (14), as well as alopecia (15). High premorbid body mass index (weight (kg)/height (m)^2)(16) and vitamin E intake (17) have been reported to be associated with a lower ALS risk. However, these variables are not known to be associated with alopecia and were therefore included in secondary analysis only. In a subanalysis, we excluded users of finasteride, a drug that blocks dihydrotestosterone production and that is used to treat enlarged prostate and alopecia; in this subanalysis, we used as baseline the date of return of the 1996 questionnaire, which was the first to inquire about finasteride use.

In total, we identified 42 cases of ALS in 565,125 person-years contributed by 40,046 men. Analyses were performed by using SAS, version 9.2, software (SAS Institute Inc., Cary, North Carolina).

RESULTS

The distribution of baseline characteristics was similar across alopecia groups (Table 1). Of the 42 participants diagnosed with ALS during the follow-up period, 13 reported no alopecia at age 45 years, 18 reported moderate alopecia, and 11 reported extensive alopecia (Table 2). The crude incidence rate of ALS increased with age as follows: below 60 years, 1.7 cases/100,000 person-years; 60–70 years, 3.0 cases/100,000 person-years; and 70 years or older, 7.1 cases/100,000 person-years. Participants reporting extensive alopecia had an almost 3-fold increased risk of ALS compared with those reporting no alopecia (relative risk adjusted for age and smoking = 2.74, 95% confidence interval: 1.23, 6.13). When additional adjustments were made for body mass index and vitamin E intake, results were similar to those observed in Table 2. Further, we observed a significant linear trend across increasing levels of balding at age 45 years and risk of ALS (P_trend = 0.02) (Table 2). When we used 5 alopecia categories instead of 3, the results were similar to those observed in Table 2. To avoid the potential influence of alopecia-associated drug use, we excluded finasteride users in a secondary analysis (2 cases among 716 users). In this analysis (which required moving the baseline from 1992 to 1996, when finasteride use was first assessed), the multivariable adjusted relative risk of ALS comparing extensive alopecia with no alopecia was 2.85 (95% confidence interval: 1.10, 7.41). Approximately 95% of participants in the Health Professionals Follow-up Study are of Caucasian descent. We
therefore performed additional analysis excluding all non-Caucasian participants (1 ALS case), but the results remained similar to the main results (relative risk = 2.44, 95% confidence interval: 1.07, 5.58).

DISCUSSION

In this large cohort of male health professionals, self-reported early-onset alopecia was associated with a higher risk of ALS. Our study benefits from prospective case ascertainment and thereby includes both slow-progressing and fast-progressing cases. Alopecia at age 45 years was self-reported retrospectively by participants aged 46–81 years; however, because participants did not have ALS at the time of exposure assessment, any differences in reporting are likely nondifferential with respect to ALS.

In this study, information on alopecia was available at age 45 years only. Further information on changes of alopecia status over time, especially alopecia assessment at an earlier age, would be of value in future studies. An important limitation of this study is the low number of ALS cases (n = 42). The results of this study should be interpreted with caution, and the hypothesis of alopecia and its association with ALS should be tested in other populations. Another limitation is that we were unable to study the risk of alopecia and ALS in different ethnic and racial groups, and further studies should be conducted to explore this association. As in all observational studies, there might be unmeasured confounding by unknown predictors of ALS.

Our results are consistent with the involvement of androgens in the etiology of ALS, a hypothesis that has been proposed previously (4, 18–20). A possible link between alopecia and ALS is the TARDBP/TDP-43 gene. In a recent meta-analysis of 7 genome-wide association studies including more than 12,800 individuals of European ancestry, a single nucleotide polymorphism (rs12565727) in the area of the ALS gene TARDBP/TDP-43 was linked to alopecia (9). This single nucleotide polymorphism was not found to be in high linkage disequilibrium (defined as $R^2 > 0.8$) with genetic variants within TARDBP/TDP-43. Linkage disequilibrium was evaluated by single nucleotide polymorphism annotation and proxy search (21). However, given their physical proximity, it is still possible for rs12565727 to influence TARDBP/TDP-43 through functional regulatory mechanisms. The TARDBP/TDP-43 gene codes for the TDP-43 protein and is involved in regulating gene expression and RNA splicing (22). Even though mutations in the TARDBP/TDP-43 gene are reported in only about 2%–5% of ALS cases (23), TDP-43–dominant protein aggregates are found in dying motor neurons in about 95% of ALS cases (22, 24, 25).

### Table 1. Age-Standardized Characteristics of Study Participants at Baseline According to Level of Balding at Age 45 Years in the Health Professionals Follow-up Study, 1992–2008

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>No Alopecia (n = 17,568 men)</th>
<th>Moderate Alopecia (n = 16,980 men)</th>
<th>Extensive Alopecia (n = 5,498 men)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Mean (SD)</td>
<td>%</td>
</tr>
<tr>
<td>Participants</td>
<td>43.9</td>
<td>42.4</td>
<td>13.7</td>
</tr>
<tr>
<td>Age in 1992, years</td>
<td>60.1 (9.6)</td>
<td>60.1 (9.7)</td>
<td>60.7 (9.9)</td>
</tr>
<tr>
<td>Body mass index$^{ab}$</td>
<td>25.4 (3.2)</td>
<td>25.4 (3.1)</td>
<td>25.7 (3.4)</td>
</tr>
<tr>
<td>Current smoker$^b$</td>
<td>9.7</td>
<td>9.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Vitamin E supplement use$^b$</td>
<td>21.2</td>
<td>20.8</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
$^a$ Calculated as weight (kg)/height (m)$^2$.
$^b$ Age-standardized value.

### Table 2. Relative Risk of Amyotrophic Lateral Sclerosis by Level of Balding in Men in the Health Professionals Follow-up Study, 1992–2008

<table>
<thead>
<tr>
<th>Level of Balding</th>
<th>No. of ALS Cases</th>
<th>Age-Adjusted Relative Risk</th>
<th>95% CI</th>
<th>Multivariate Relative Risk$^a$</th>
<th>95% CI</th>
<th>Multivariate Relative Risk$^b$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No alopecia</td>
<td>13</td>
<td>1.00</td>
<td>Referent</td>
<td>1.00</td>
<td>Referent</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Moderate alopecia</td>
<td>18</td>
<td>1.45</td>
<td>0.71, 2.97</td>
<td>1.47</td>
<td>0.72, 2.99</td>
<td>1.44</td>
<td>0.71, 2.95</td>
</tr>
<tr>
<td>Extensive alopecia</td>
<td>11</td>
<td>2.69</td>
<td>1.20, 6.01</td>
<td>2.74</td>
<td>1.23, 6.13</td>
<td>2.75</td>
<td>1.23, 6.15</td>
</tr>
</tbody>
</table>

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval.
$^a$ Adjusted for age (in single years) and smoking status (current, previous, or never).
$^b$ Adjusted for age (in single years), smoking status (current, previous, or never), body mass index (weight (kg)/height (m)$^2$) (in categories of underweight, normal, overweight, and obese), and vitamin E supplement use (yes or no).

Neither the cause of ALS nor the cause of alopecia is fully understood. Although the presence of dihydrotestosterone is required for the development of alopecia (8), circulating levels of dihydrotestosterone have not been shown to be associated with alopecia. Rather, it is the sensitivity of androgen receptors, pairing with dihydrotestosterone in hair follicles, that is thought to be the cause (8). This process is regulated by several coactivators and corepressors (8). We speculate that androgen receptor sensitivity might play a role in ALS etiology as well, possibly with the involvement of TDP-43 protein abnormalities. In conclusion, we found an association between early-onset alopecia and ALS. The mechanisms underlying this association deserve further investigation.

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