LETTERS

Job-related formaldehyde exposure and ALS mortality in the USA

Animal models and in vitro experiments suggest neurotoxic effects of formaldehyde that may be relevant for amyotrophic lateral sclerosis (ALS). Formaldehyde induces neuronal τ-protein misfolding and aggregation, leading to neuronal apoptosis. Formaldehyde also increases mitochondrial membrane permeability and causes oxidative damage partly by reducing superoxide dismutase activity, mechanisms implicated in ALS.

Studies have had mixed findings regarding formaldehyde exposure and ALS mortality. A large prospective study found an elevated risk that did not quite reach statistical significance, but found a strong dose–response relationship with total years of exposure. Two studies found no significant association, although one found a suggestion of elevated risk among the very highly exposed. We examine here the association of ALS mortality with job-related formaldehyde exposure in the National Longitudinal Mortality Study (NLMS), a US-representative cohort with occupation data collected prospectively.

METHODS

The NLMS is a multistage probability sample of the civilian non-institutionalised population (response rate ~96%). We included the 794,541 men and 674,694 women who were at ages 25+ when surveyed. Participants were asked about their current or most recent job. We used a formaldehyde exposure matrix constructed by industrial hygienists at the National Cancer Institute and previously described. Intensity and probability of formaldehyde exposure were calculated for each occupation and industry, and coded as none, low, medium or high. Intensity reflected the frequency and level of formaldehyde exposure; probability reflected the likelihood of any formaldehyde exposure.

NLMS records were matched to the National Death Index (NDI, 1979–2011) to obtain cause of death. ALS deaths were defined as International Classification of Diseases Ninth and 10th Edition (ICD)-9 335.2 or ICD-10 G12.2 as the underlying cause. Data were handled to obtain cause of death. ALS deaths were coded as none, low, medium or high probability formaldehyde exposure, with exclusion of any formaldehyde exposure.

RESULTS

Participants exposed versus unexposed to formaldehyde were slightly poorer, less educated, and less frequently non-Hispanic White (see online supplementary eTable S1). High probability of formaldehyde exposure versus no exposure predicted an almost three times higher rate of ALS mortality in men (table 1). Among women, few had high-exposure-probability jobs and there were no ALS deaths in this category; so the HR was inestimable (see online supplementary eTable S2). Intensity of formaldehyde exposure was less strongly associated with ALS (table 1). High-probability, high-intensity exposure was associated in men with increased rate of ALS mortality (HR=4.43, 95% CI 1.16 to 16.85, p<0.05), although there were only two ALS deaths among these highly exposed men. Results were robust to further adjustment for military service and smoking. All men with high-probability, high-intensity exposure were funeral directors. Among men, all sensitivity analyses resulted in higher HR estimates than the main analysis (table 1).

DISCUSSION

Men in jobs with high probability of exposure versus no formaldehyde exposure had almost three times greater rate of ALS mortality. We did not find increased risk of ALS in women associated with formaldehyde exposure. Only 99 women in our sample reported jobs with high-probability, high-intensity formaldehyde exposure; thus, our sample of exposed women may have been too small to detect a possible increased risk of ALS. Moreover, all men (N=493) and all but one woman (99%, N=98) in our study in jobs with high-probability high-intensity formaldehyde exposure were funeral directors. In the USA, female versus male funeral directors are more likely to interact with bereaved clients and less likely to perform embalming, where exposure to formaldehyde occurs. Thus, formaldehyde exposure may vary by sex in this profession.

Two prior studies found no association of ALS with job-related formaldehyde exposure. A study of garment workers (geometric mean formaldehyde exposure=0.15 ppm) found no elevated ALS mortality compared with the general population. As garment work does not involve high-probability or high-intensity exposure, these results may not be inconsistent with ours. Funeral directors experience high-intensity and high-probability formaldehyde exposure, with exposure ranging from 0.15 to 9.2 ppm during embalming. Additionally, formaldehyde is absorbed through the skin during embalming (at 49.2 mg/h). A second study found no overall association between estimated occupational formaldehyde exposure and ALS. However, in the small subset of participants with the highest exposure to formaldehyde (>60 000 h, N=4 cases, N=4 controls), a large, non-statistically-significant odds for ALS was found (OR=3.0, 95% CI 0.7 to 12.9).

Our results should be interpreted cautiously. Jobs involving both high probability and high intensity of formaldehyde are relatively uncommon in the USA, and ALS is also rare; there were only two ALS deaths among men in such jobs. Moreover, we did not find a dose–response association between formaldehyde exposure and ALS. Formaldehyde exposure was estimated from a single report at enrolment. This single job report likely did not accurately capture lifetime exposure. As non-differential error in exposure classification typically leads to attenuation of the true association of exposure with disease, our estimated HRs could have been attenuated and any trend obscured.

In addition to formaldehyde, funeral directors are exposed to other chemicals used in embalming, as well as to viral, bacterial and prion pathogens. Thus, further study of the association of ALS with high...
levels of formaldehyde exposure and among funeral directors is warranted.

Table 1 Adjusted HRs* and 95% CIs for ALS mortality by level of occupational formaldehyde exposure, National Longitudinal Mortality Study, men ages 25 years and older, 1973–2011

<table>
<thead>
<tr>
<th>Intensity, exposed restricted to probability=high</th>
<th>Respondents</th>
<th>Person-years</th>
<th>ALS deaths</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>607 416</td>
<td>9 815 195</td>
<td>372</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>97 301</td>
<td>1 641 068</td>
<td>55</td>
<td>0.99 (0.74 to 1.30)</td>
</tr>
<tr>
<td>Medium</td>
<td>86 766</td>
<td>1 427 789</td>
<td>43</td>
<td>0.63 (0.44 to 0.90)</td>
</tr>
<tr>
<td>High</td>
<td>3058</td>
<td>46 188</td>
<td>2</td>
<td>1.53 (0.40 to 5.80)</td>
</tr>
</tbody>
</table>

Probability, respondents 35≤age≤75 at enrolment

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Respondents</th>
<th>Person-years</th>
<th>ALS deaths</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>492 489</td>
<td>9 501 370</td>
<td>331</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>82 155</td>
<td>1 637 260</td>
<td>47</td>
<td>0.87 (0.64 to 1.18)</td>
</tr>
<tr>
<td>Medium</td>
<td>71 598</td>
<td>1 372 603</td>
<td>39</td>
<td>0.77 (0.54 to 1.10)</td>
</tr>
<tr>
<td>High</td>
<td>758</td>
<td>15 230</td>
<td>2</td>
<td>3.49 (0.92 to 13.26)</td>
</tr>
</tbody>
</table>

Probability, follow-up to age 75 only

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Respondents</th>
<th>Person-years</th>
<th>ALS deaths</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>604 116</td>
<td>9 794 521</td>
<td>332</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>97 959</td>
<td>1 680 822</td>
<td>41</td>
<td>0.79 (0.57 to 1.11)</td>
</tr>
<tr>
<td>Medium</td>
<td>86 760</td>
<td>1 407 671</td>
<td>40</td>
<td>0.66 (0.44 to 0.99)</td>
</tr>
<tr>
<td>High</td>
<td>832</td>
<td>15 315</td>
<td>2</td>
<td>4.13 (1.09 to 15.69)</td>
</tr>
</tbody>
</table>

Probability, respondents 35≤age≤75 at enrolment

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Respondents</th>
<th>Person-years</th>
<th>ALS deaths</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>427 530</td>
<td>6 493 151</td>
<td>332</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>65 736</td>
<td>1 046 575</td>
<td>47</td>
<td>0.91 (0.67 to 1.24)</td>
</tr>
<tr>
<td>Medium</td>
<td>60 675</td>
<td>921 096</td>
<td>43</td>
<td>0.79 (0.56 to 1.12)</td>
</tr>
<tr>
<td>High</td>
<td>568</td>
<td>9731</td>
<td>2</td>
<td>3.41 (0.89 to 13.01)</td>
</tr>
</tbody>
</table>

Probability, respondents employed at enrolment

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Respondents</th>
<th>Person-years</th>
<th>ALS deaths</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>548 645</td>
<td>8 876 712</td>
<td>331</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>85 041</td>
<td>1 459 452</td>
<td>45</td>
<td>0.88 (0.65 to 1.21)</td>
</tr>
<tr>
<td>Medium</td>
<td>76 249</td>
<td>1 238 082</td>
<td>38</td>
<td>0.71 (0.50 to 1.03)</td>
</tr>
<tr>
<td>High</td>
<td>770</td>
<td>14 063</td>
<td>2</td>
<td>3.26 (0.86 to 12.38)</td>
</tr>
</tbody>
</table>

*Adjusted for race/ethnicity, education and household income as a percentage of the poverty line.

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Disclosures This paper is released to inform interested parties of research and to encourage discussion. Any views expressed on statistical, methodological, technical, or operational issues are those of the authors and not necessarily those of the US Census Bureau.

Contributors All authors made substantial contributions to the conception or design of the work, or to the acquisition, analysis or interpretation of data for the work, to the drafting of the manuscript or revised it critically for important intellectual content; and approved the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. NJJ had full access to the data and takes responsibility for accuracy of the data analyses.

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