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Letters to the Editor

RE: "AMYOTROPHIC LATERAL SCLEROSIS AND EXPOSURE TO DIESEL EXHAUST IN A DANISH COHORT"

I am writing to praise the strengths of Dickerson et al.'s (1) study of amyotrophic lateral sclerosis (ALS) and diesel exhaust (DE) as well as to raise some issues with it. Several points and results in the study were left with no scientific explanations, and scientific and logical assumptions were made about these points. I offer some suggestions that could be followed in future studies for potentially more stable results.

Overall, Dickerson et al. did a good job explaining the study design and analysis. However, there is a discrepancy between Figure 1 (1) and the article when defining cases and controls. Individuals born before 1939 were excluded, as noted in Figure 1 (1). However, the article notes that individuals born in 1940 or earlier were excluded (1), and this difference of a year could have affected the overall case/control number.

Table 1 illustrates the characteristics of cases of amyotrophic lateral sclerosis and controls (1). However, in the figure, female population data is not defined until the last row. Although the female-to-male ratio is skewed toward men (1), it might be valuable to include women in the characteristics table to compare exposure differences between men and women.

The study did not adjust for exposure to formaldehyde, one of the main DE components, as mentioned in the article. Formaldehyde can be found in cosmetic products such as shampoos, lotions, and soap (2). Not adjusting for formaldehyde exposure could be due to a limitation in the records that were used, and it could lead to misclassification.

The data were also stratified according to sex due to traditional roles of men and women when it comes to careers. Another strength of the study is the authors' awareness of ways that societal gender differences might cause results to deviate from the desired objective. However, the data did not take into account whether any of the industries provided their employees with personal protective equipment, such as safety masks and gloves.

The researchers analyzed the data using 2 different ways to calculate exposure. That enabled them to find different, significant results for each exposure. However, among women, the odds ratio was 0.58 (1), which was contrary to their expectations and underestimated their other findings. The reduced odds ratio was a "chance finding" (1, p. 1618). However, that could be due to a confounding variable that the analysis did not adjust for. For example, women might have been more likely to work in offices or other workplaces that made them less likely to be exposed to high amounts of DE, and men might have been more likely to have worked in places closer to DE emissions, therefore having higher exposure. In other words, the researchers could have done a better job adjusting the data for confounding variables.

The study, to my knowledge and that of Dickerson et al. (1, p. 1619), is the first of its kind. Thus, further studies are warranted, taking into consideration several points to avoid distorted results. These points involve adjusting for: 1) the most common, daily-use products containing formaldehyde; 2) protective measures, such as safety masks, that are applied in some industries but not others; and 3) the tasks that are assigned to each participant in each industry to determine how much they are subjected to DE. These are all points that could result in misclassification among exposed and unexposed subjects.

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Conflict of interest: none declared.

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THE AUTHORS REPLY

We appreciate Alquwayfili's (1) interest in our article on occupational exposure to diesel exhaust (DE) and amyotrophic lateral sclerosis (ALS) in Denmark (2). First, we thank him for pointing out our error in the last paragraph of the methods (2). We excluded those who were born at least 25 years prior to 1964, the year the registry was established. Thus, the exclusion was birth year before 1939, which is the cutoff that was used throughout the analysis; all the numbers shown in the figure and tables are correct (1).

Alquwayfili raises an interesting point about formaldehyde. As a component of DE, it is possible that formaldehyde

exposure could account for our findings for DE given that we have found that formaldehyde exposure is associated with amyotrophic lateral sclerosis (3, 4), including in a study of occupational exposures to formaldehyde in these Danish registries (5). Importantly though, the formaldehyde job-exposure matrix (JEM) does not consider DE-exposed industries as formaldehyde-exposed, and there is no overlap between the exposed jobs in the 2 JEMs. The possibility of confounding by formaldehyde from exposures related to use of cosmetic products (data that is not in the Danish registries) is unlikely—it is not clear why that use would be associated with DE-exposed occupations, which would be needed for confounding. Further, such use would not result in misclassification of DE exposure.

We appreciate the acknowledgement of our consideration of differences by sex in the workplace (1). We stratified the analysis by sex to account for potential differences in job tasks and subsequent exposures, such as those Alquwayfili describes, which would appear as effect measure modification, but the stratification also addresses potential confounding by sex.

The issue of personal protective equipment use is certainly a good one, but that kind of data is very difficult to maintain in very large data sets like those of the Registries, a limitation we noted in the limitations section of our manuscript (1). It is important to note, however, that the JEM we used was developed by a team of exposure experts with information covering over 300 occupational categories (6). DE exposure was characterized by 2 measures: the probability of exposure and the mean level of exposure. Probability measures are based on estimates from survey data assessing risk of DE exposure, including technological advances in machinery and use of personal protective equipment in each industry (6). While we believe the significantly protective association seen among women was the result of chance—there was no consistent pattern to that finding as there was with the results in men—we cannot rule out uncontrolled confounding. But what Alquwayfili describes would not cause a confounded result, because it relates to differences in exposure by sex, while the finding was a comparison among women only.

In conclusion, we appreciate the interest in our manuscript. Certainly there are additional data that could help improve on our findings, which might be relevant to current workers in DE-exposed industries and potentially other populations with high and consistent exposures to DE. The difficulty is that such data are often hard to come by in large enough populations for studies of amyotrophic lateral sclerosis.

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RE: "ASSOCIATIONS OF DIETARY PROTEIN INTAKE WITH FAT-FREE MASS AND GRIP STRENGTH: A CROSS-SECTIONAL STUDY IN 146,816 UK BIOBANK PARTICIPANTS"

We read with interest the article by Celis-Morales et al. (1), who concluded that there is a positive association of dietary protein intake with both fat-free body mass percentage and handgrip strength, on the basis of data from the UK Biobank.

We are concerned that the positive association observed might have been attributable to expressing the exposure—dietary protein intake—in grams per kilogram of body weight per day (g/kg/day). Dividing protein intake by body weight meant that participants in the top category of protein intake were people who had a high protein intake relative to their body weight, and vice versa for those in the lowest category. This approach results in participants in the top category being mostly people with a low body weight. Because of the inevitable positive correlation of body weight with body fat percentage, participants with a low body weight have a low body fat percentage. Consequently, it might be expected that participants with a high