Reproductive History and Age of Onset for Women Diagnosed with Amyotrophic Lateral Sclerosis: Data from the National ALS Registry: 2010–2018

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**Keywords**
Amyotrophic lateral sclerosis · Motor neuron disease · Females · Menopause · Reproductive history

**Abstract**

**Background:** Amyotrophic lateral sclerosis (ALS) is a neurological disease of largely unknown etiology with no cure. The National ALS Registry is a voluntary online system that collects demographic and reproductive history (females only) data from patients with ALS. We will examine the association between demographic and reproductive history among female patients aged >18 years and various ages of onset for ALS.

**Methods:** Data from a cross-sectional study were collected and examined for 1,018 female ALS patients. Patient characteristics examined were demographics including race, BMI, and familial history of ALS. Among patients, information on reproductive history, including age at menopause, ever pregnant, and age at first pregnancy was collected. Unadjusted and adjusted logistic regression models were used to estimate OR and 95% CI in this study.

**Results:** Women were more likely to be diagnosed with ALS before age 60 if they were nonwhite ($p = 0.015$), had attended college ($p = 0.0012$), had a normal BMI at age 40 ($p < 0.0001$), completed menopause before age 50 ($p < 0.0001$), and had never been pregnant ($p = 0.046$) in the univariate analysis. Women diagnosed with ALS before age 60 were also more likely to have limb site of onset ($p < 0.0001$). In the multivariate analysis, those who completed menopause before age 50 were more likely to be diagnosed with ALS before age 60 (OR = 1.8, 95% CI: 1.4–2.3) compared with women who completed menopause at or after age 50, after controlling for race, ever pregnant, age at first pregnancy, family history of ALS, education status, smoking history, and BMI at age 40.

For women who were diagnosed with ALS before age 50, the odds of them entering menopause before age 50 climb to 48.7 (95% CI: 11.8, 200.9). The mean age of ALS diagnosis for women who completed menopause before age 50 was 58 years and 64 years for women who entered menopause after age 50 ($p < 0.0001$).

**Conclusion:** Women who reported completing menopause before age 50 were significantly more likely to be diagnosed with ALS before age 60 compared with those who reported entering menopause after age 50. More research is needed to determine the relationship between female reproductive history, especially regarding endogenous estrogen exposure and early-onset ALS.

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Female Reproductive History and Age of Onset for ALS Diagnosis

Introduction

Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease defined by the loss of upper and lower motor neurons, typically resulting in death within 2–5 years from disease [1]. Conservative estimates suggest that in the USA, over 16,000, or 5.2/100,000 people lived with ALS in 2015 [2] and approximately 5,000, or 1.5/100,000 are diagnosed annually [3]. Familial ALS, a hereditary form of the disease, accounts for 5–10% of cases, whereas the remaining cases have no clearly defined etiology [1]. Motor neuron degeneration in nonheredity ALS is considered to be a multifactorial process, consisting of both genetic and environmental factors [4, 5]. Currently, there is no cure for ALS, so understanding the pathogenic factors may help provide ways to slow down progression of the disease or even find a cure.

National surveillance and epidemiologic studies have shown a slightly lower prevalence of ALS in women compared with men (40 vs. 60%) [2, 6]. This suggests a possible protective effect of female reproductive hormones pertaining to ALS [7]. The association between ALS and female reproductive hormones such as estrogen has been studied using female hormonal factors such as age of menopause and menarche [7, 8]. Many of these studies are case-control studies with a small number of women with ALS.

Here, we examine associations of female reproductive history and early age at ALS onset, defined as being diagnosed before age 60, in a large cohort of US participants enrolled in the National ALS Registry. The registry is the largest population registry for ALS in the USA [3]. Advantages of using cases from this registry include the wide phenotypic differences in a national population [9, 10]. Having a better understanding of ALS risk factors pertaining to female reproductive history and age of diagnosis may provide more insights into disease mechanisms and assist clinicians in making more rapid diagnoses, which could lead to earlier therapeutic interventions.

Methods

The National ALS Registry

In October 2010, the US Federal Agency for Toxic Substances and Disease Registry (ATSDR), an environmental health agency administratively linked to the Centers for Disease Control and Prevention (CDC), launched the congressionally mandated, population-based National ALS Registry to help clarify the epidemiology of ALS in the USA [11]. While details about the registry’s objectives are presented elsewhere [2], in brief, the registry’s purpose is to quantify the incidence and prevalence of ALS in the USA, describe the patient demographics, and examine potential risk factors [12]. Similarly, the registry’s methods also have been previously described [13]. Cases from both the national administrative databases and the web portal are merged and deduplicated to ensure that individuals are not counted twice. To verify ALS status within the web portal, ATSDR adopted the 6 questions from the US Department of Veterans Affairs ALS registry that have been proven to be reliable indicators for accurate ALS diagnoses [14].

The registry’s web portal also allows participants to complete brief online surveys about their ALS risk factors and experience on topics such as demographics, prediagnosis symptoms, and female reproductive history. Currently, there are 17 survey modules available as shown in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000516344) [15]. These surveys were designed by the ALS Consortium of Epidemiologic Studies (ACES) at Stanford University [16, 17] and are structured such that participants can answer the questions without having to involve a healthcare provider. Due to the nature of these online surveys, it is likely there is a self-selection bias as well as recall bias within the study. These data are likely slanted toward a younger and better educated patient sample, possibly skewing our results more away from the null hypothesis [18]. We were able to capture the highest level of education completed for the women in the study and include it in the analyses. To date, almost 100,000 surveys have been completed representing the largest, most geographically diverse collection of ALS risk factor data available.

Hormonal and Reproductive History Survey Module

The hormonal and reproductive history survey module was launched on August 1, 2014. The purpose of the module is to examine the female patients’ reproductive histories throughout their lifetime up to and after diagnosis. The survey contains 10 questions and covers time periods of menarche, pregnancy, and menopause as shown in online suppl. Table 2 [19]. As the module was not initiated from the start of the registry, all participants were able to log back in and partake in the survey. Participation was voluntary, and only women who responded to the questions were used in the analysis (e.g., if a woman did not respond to a question about family history of ALS, she would have missing information for that variable). Therefore, this analysis covers from October 19, 2010, to December 31, 2018, and the most recent year data were available.

Data Analysis

Selected demographic characteristics including race, age at diagnosis, BMI, and family history were abstracted for those who completed the hormonal and reproductive history survey module. Due to the high percentage of white participants, race was classified as white or nonwhite. If >1 race was selected, participants were categorized as nonwhite. BMI was calculated using the standard formula: BMI = weight (lb)/[height (in)]^2 × 703 [20]. In the USA, the mean age of menopause is 51 [21], so the main predictor variable for this analysis was age at menopause (<50 vs. 50 years and older); a small number of women under age 50 still having menses were excluded from this part of the analysis. The definition used in this analysis for menopause was 12 months after the last menstrual period for those undergoing natural menopause. For those women undergoing artificial menopause, the age given in the survey was used for menopause. The outcome variable was age at ALS diagnosis. Age 60 was used to define early diagnosis because while ALS can affect people at any age, sporadic cases typically start
Table 1. Characteristics among US women with ALS who responded to the National ALS Registry's Hormonal and Reproductive History Survey (October 19, 2010, to December 31, 2018)

| Characteristic                        | Diagnosis age <60 yr | Diagnosis age ≥60 yr | p value |
|---------------------------------------|----------------------|-----------------------|---------|
|                                       | N = 515              | %                     | N = 503 | %       |
| Diagnosis year                         |                      |                       |         |         |
| Before 2014                            | 107                  | 20.8                  | 69      | 13.7    |
| 2014                                  | 92                   | 17.9                  | 85      | 16.9    |
| 2015                                  | 101                  | 19.6                  | 110     | 21.9    |
| 2016                                  | 104                  | 20.2                  | 101     | 20.1    |
| 2017                                  | 65                   | 12.6                  | 76      | 15.1    |
| 2018                                  | 46                   | 8.9                   | 62      | 12.3    |
| Race                                  |                      |                       |         |         |
| White                                 | 486                  | 94.4                  | 490     | 97.4    |
| Nonwhite                              | 29                   | 5.6                   | 13      | 2.6     |
| BMI at registration                   |                      |                       |         |         |
| Underweight/normal                    | 187                  | 36.6                  | 226     | 45.2    |
| Overweight/obesity                    | 324                  | 63.4                  | 274     | 54.8    |
| BMI at age 40                          |                      |                       |         |         |
| Underweight/normal                    | 206                  | 43.4                  | 284     | 56.9    |
| Overweight/obesity                    | 269                  | 56.6                  | 215     | 43.1    |
| Highest education                     |                      |                       |         |         |
| Did not complete high school          | 17                   | 3.3                   | 33      | 6.5     |
| High school diploma/GED               | 70                   | 13.6                  | 104     | 20.6    |
| Trade school completion               | 34                   | 6.6                   | 19      | 3.8     |
| Some college credit                   | 102                  | 19.8                  | 93      | 18.4    |
| College degree                        | 199                  | 38.6                  | 155     | 30.7    |
| Postgraduate degree                   | 93                   | 18.1                  | 99      | 19.6    |
| Smoking status                         |                      |                       |         |         |
| Never smoker                          | 303                  | 59.6                  | 272     | 54.3    |
| Ever smoker                           | 205                  | 40.4                  | 228     | 45.5    |
| Age at first menstrual cycle          |                      |                       |         |         |
| 12 yr or older                        | 177                  | 37.1                  | 265     | 54      |
| <12 yr                                | 300                  | 62.9                  | 226     | 46      |
| Age at menopause                      |                      |                       |         |         |
| 50 yr or older                        | 158                  | 35.4                  | 297     | 54.2    |
| <50 yr                                | 288                  | 64.6                  | 251     | 45.8    |
| Ever pregnant                         |                      |                       |         |         |
| Yes                                   | 440                  | 85.5                  | 454     | 90.3    |
| No                                    | 74                   | 14.5                  | 49      | 9.7     |
| Pregnancies, n                        |                      |                       |         |         |
| 1                                     | 61                   | 13.9                  | 65      | 14.3    |
| 2                                     | 151                  | 34.4                  | 151     | 33.3    |
| 3                                     | 117                  | 36.7                  | 128     | 28.2    |
| 4                                     | 64                   | 14.6                  | 51      | 11.2    |
| 5 or more                             | 46                   | 10.5                  | 59      | 13      |
| Age at first pregnancy                 |                      |                       |         |         |
| <30 yr                                | 351                  | 79.6                  | 385     | 84.8    |
| 30 yr or older                        | 90                   | 20.4                  | 69      | 15.2    |
| Age at last pregnancy                  |                      |                       |         |         |
| <35 yr                                | 351                  | 79.6                  | 363     | 80      |
| 35 yr or older                        | 90                   | 20.4                  | 91      | 20      |
| Family history of ALS                 |                      |                       |         |         |
| Sporadic ALS                          | 475                  | 92.2                  | 468     | 93      |
| Familial ALS                          | 40                   | 7.8                   | 35      | 7       |

χ² analysis with statistical significance at p < 0.05. ALS, amyotrophic lateral sclerosis.
Female Reproductive History and Age of Onset for ALS Diagnosis

Table 2. Initial site of onset among US women with ALS who responded to the National ALS Registry’s Hormonal and Reproductive History Survey (October 19, 2010, to December 31, 2018)

| Characteristic         | Diagnosis age <60 yr | Diagnosis age ≥60 yr | Total     | p value |
|------------------------|----------------------|----------------------|-----------|---------|
|                        | N = 373              | N = 382              | N = 755   |         |
| Symptom onset site*    |                      |                      |           |         |
| Limb                   | 284                  | 227                  | 511       | 67.7    | <0.0001 |
| Arm or hand            | 118                  | 94                   | 212       | 28.1    | 0.0317  |
| Leg or foot            | 166                  | 133                  | 299       | 39.6    | 0.0065  |
| Bulbar                 | 75                   | 138                  | 213       | 28.2    | <0.0001 |
| Trunk/global           | 14                   | 17                   | 31        | 4.1     | 0.6295  |

χ² analysis with statistical significance at p < 0.05. ALS, amyotrophic lateral sclerosis. * Initial site of onset refers to the first body region where a patient reported a weakness or symptom prior to ALS diagnosis. The main categories for symptom onset are in bold. Arm and leg are subcategories.

Results

Between October 19, 2010, and December 31, 2018, 3,207 women, 18 years or older, registered via the registry’s online portal and completed at least one of the 17 surveys. Of these, 1,018 (31.7%) completed the hormonal and reproductive survey module as well as basic demographic information. Demographic characteristics of these 1,018 females are displayed in Table 1. Some 503 women were diagnosed with ALS after age 60 of the 1,018 participants in the study (49.5%). Of the women diagnosed before age 60, they were more likely to have a higher BMI at age 40, attended college or higher, and never have been pregnant (Table 1). Almost 65% of the women diagnosed before age 60 entered menopause before age 50 (Table 1).

Site of onset among the 755 women who provided this information stratified by age of diagnosis (<60 years vs. at or >60 years) is presented in Table 2. All participants reported having progressive muscle weakness prior to ALS diagnosis. Just over two-thirds of participants (n = 511) had limb onset. Women diagnosed before age 60 were more likely to have had limb-onset weakness (p < 0.0001) and weakness first in their leg or foot (p = 0.0065). Approximately 28% of the 755 participants experienced bulbar onset; of those, women diagnosed at or after age 60 were statistically more likely to have bulbar onset (p < 0.0001). Trunk/global onset accounted for 4.1% of participants with an even distribution among diagnosis age groups.

Other symptoms experienced are presented in Table 3. The most frequent symptoms included muscle cramps (59.7%), fasciculations (50.5%), and dysarthria (38.6%). Approximately one-fourth (n = 189) had experienced trips or falls. Almost 16% of participants had difficulty controlling bowels, 3.5% had experienced pneumonia, and 2.9% experienced blood clots. When stratified by age group at diagnosis, a higher proportion of women diagnosed before age 60 reported suffering from twitching (p = 0.0003) as well as cramps (p = 0.0452).

The crude OR for being diagnosed with ALS before age 60 for women who entered menopause before age 50 compared with those who entered menopause at or after age 50 was 2.0 (95% CI: 1.5, 2.6) (Table 4). For the multivariate analysis, backward elimination was used to establish the
Table 3. Other symptoms experienced among 1,018 US women with ALS who responded to the National ALS Registry’s Hormonal and Reproductive History Survey (October 19, 2010, to December 31, 2018)

| Other symptoms (Have you ever experienced the following?) | Diagnosis age <60 yr | Diagnosis age ≥60 yr | Total | χ² | p value |
|----------------------------------------------------------|-----------------------|-----------------------|-------|----|---------|
|                                                          | n         | %       | n         | %       | n         | %       |       |    |         |
| Pneumonia                                                | 12        | 3.2     | 14        | 3.7     | 26        | 3.5     | 0.5676 |    |          |
| Falls                                                    | 96        | 25.9    | 93        | 24.5    | 189       | 25.2    | 0.2138 |    |          |
| Blood clot                                               | 10        | 2.7     | 12        | 3.2     | 22        | 2.9     | 0.5582 |    |          |
| Cramps                                                   | 222       | 53.5    | 193       | 50.7    | 415       | 59.7    | 0.0452 |    |          |
| Twitching (fasciculations)                               | 215       | 58.0    | 164       | 43.2    | 379       | 50.5    | 0.0003 |    |          |
| Problems with speech (dysarthria)                        | 126       | 34.2    | 163       | 42.9    | 289       | 38.6    | 0.0464 |    |          |
| Difficulty controlling bowels                            | 59        | 16.0    | 57        | 15.0    | 116       | 15.5    | 0.8881 |    |          |

χ² analysis statistically significant at p < 0.05. ALS, amyotrophic lateral sclerosis.

Table 4. Logistic regression analyses for an ALS diagnosis before age 60 for women, October 19, 2010, to December 31, 2018

| Variable                      | Parameter estimate | p value | OR | 95% CI  |
|-------------------------------|--------------------|---------|----|---------|
| Age at menopause              | 0.6868             | <0.0001 | 2.0| (1.5, 2.6) |

| Variable                      | Parameter estimate | p value | OR | 95% CI  |
|-------------------------------|--------------------|---------|----|---------|
| Age at menopause              | 0.6064             | <0.0001 | 1.8| (1.4, 2.4) |
| Age at first pregnancy        | 0.4913             | 0.0091  | 1.6| (1.1, 2.4) |
| BMI at age 40                 | 0.4107             | 0.004   | 1.5| (1.1, 2.1) |

GEE analysis with significance at p < 0.05. ALS, amyotrophic lateral sclerosis. * Unadjusted model. * Adjusted model, covariates include race, education level, smoking status, age of first menstruation, ever pregnant, number of pregnancies, age at last pregnancy, heredity, site of onset, and BMI at registration. a Referent = completed menopause at or after age 50. b Referent = first pregnancy was before age 30. c Referent = normal or underweight.

Table 5. Logistic regression analyses for an ALS diagnosis before age 50 for women, October 19, 2010, to December 31, 2018

| Variable                      | Parameter estimate | p value | OR | 95% CI  |
|-------------------------------|--------------------|---------|----|---------|
| Age at menopause (ALS dx age <50) | 3.7991             | <0.0001 | 44.7| (14.1, 141.5) |

| Variable                      | Parameter estimate | p value | OR | 95% CI  |
|-------------------------------|--------------------|---------|----|---------|
| Age at menopause (ALS dx age <50) | 3.8858             | <0.0001 | 48.7| (11.8, 200.9) |
| Age at first pregnancy        | 0.6797             | 0.0295  | 2.0| (1.1, 3.6) |
| BMI at age 40                 | 0.6406             | 0.0129  | 1.9| (1.1, 3.1) |
| Education level              | 0.9834             | 0.0035  | 2.7| (1.4, 5.2) |

GEE analysis with significance at p < 0.05. ALS, amyotrophic lateral sclerosis. * Unadjusted model. * Adjusted model, covariates include race, smoking status, age of first menstruation, number of pregnancies, age at last pregnancy, ever pregnant, family history of ALS, site of onset, and BMI at registration. a Referent = completed menopause at or after age 50. b Referent = first pregnancy was before age 30. c Referent = normal or underweight. d Referent = less than college level courses taken.
final reduced logistic regression model. In this model, adjustments for age at first pregnancy, whether a woman was ever pregnant, and having a high BMI (overweight/obese) at age 40 lowered this association slightly (OR = 1.8, 95% CI: 1.4, 2.3). Several variables showed a significant association with being diagnosed with ALS before age 60: age at first pregnancy (OR = 1.6, 95% CI = 1.3, 1.9, p = 0.0029), whether a woman was ever pregnant (OR = 1.6, 95% CI = 1.1, 2.5, p = 0.0011), and being overweight/obese at age 40 (OR = 1.6, 95% CI = 1.3, 2.1, p = 0.0002). In general, women completing menopause before age 50, experiencing first pregnancy at or after age 30, not being pregnant, and having a high BMI (overweight/obese) at age 40 were more likely to be diagnosed with ALS before age 60 compared to their counterparts (Table 4).

Shifting the age at an ALS diagnosis to <50 years, from 60 years, increased the crude OR dramatically (OR = 44.7, 95% CI: 14.1, 141.5) (Table 5). In this model, adjustments for age at first pregnancy, having overweight/obesity, and highest education level raised this association slightly (OR = 48.7, 95% CI: 11.8, 200.9), and other adjustments were not statistically significant. The 3 variables that were significantly associated with an ALS diagnosis before age 50 were age at first pregnancy (OR = 2.1, 95% CI = 1.1, 3.8, p = 0.0138), having overweight/obesity at age 40 (OR = 2.1, 95% CI = 1.3, 3.3, p = 0.0028), and attending college or higher (OR = 2.7, 95% CI = 1.4, 5.2). In general, women completing menopause before age 50, experiencing first pregnancy at or after age 30, not being pregnant, having a high BMI (overweight/obese) at age 40, and attending college or higher were more likely to be diagnosed with ALS before age 50 compared to their counterparts (Table 5).

Table 6. Mean age at diagnosis by reproductive risk factors, among US women* with ALS who responded to the National ALS Registry’s Hormonal and Reproductive History Survey (October 19, 2010, to December 31, 2018)

| Variable                          | N   | Mean age of diagnosis | 95% CI       | Pooled Pr > |t| |
|-----------------------------------|-----|-----------------------|--------------|-------------|--------|
| Menopause                         |     |                       |              |             |        |
| <50 yr old                        | 526 | 58.4 (57.4, 59.4)     | (57.4, 59.4) | <0.0001     |        |
| ≥50 yr old                        | 442 | 64.0 (63.4, 64.7)     | (63.4, 64.7) |             |        |
| Age at menstruation               |     |                       |              |             |        |
| <12 yr old                        | 181 | 61.8 (60.2, 63.3)     | (60.2, 63.3) | 0.0073      |        |
| ≥12 yr old                        | 837 | 60.2 (59.5, 61.0)     | (59.5, 61.0) |             |        |
| Ever pregnant                     |     |                       |              |             |        |
| Yes                               | 894 | 61.0 (60.3, 61.7)     | (60.3, 61.7) | 0.0002      |        |
| No                                | 123 | 57.2 (55.2, 59.3)     | (55.2, 59.3) |             |        |
| Age at first pregnancy            |     |                       |              |             |        |
| <30 yr old                        | 736 | 61.4 (60.7, 62.2)     | (60.7, 62.2) | 0.0029      |        |
| ≥30 yr old                        | 159 | 58.8 (57.2, 60.3)     | (57.2, 60.3) |             |        |
| Age at last pregnancy             |     |                       |              |             |        |
| <35 yr old                        | 714 | 61.0 (60.2, 61.7)     | (60.2, 61.7) | 0.9693      |        |
| ≥35 yr old                        | 181 | 60.9 (59.5, 62.4)     | (59.5, 62.4) |             |        |
| Family history of ALS             |     |                       |              |             |        |
| No                                | 943 | 60.6 (60.0, 61.3)     | (60.0, 61.3) | 0.1998      |        |
| Yes                               | 75  | 59.0 (56.4, 61.6)     | (56.4, 61.6) |             |        |
| BMI at age 40                     |     |                       |              |             |        |
| Underweight/normal                | 490 | 62.9 (62.1, 63.7)     | (62.1, 63.7) | <0.0001     |        |
| Overweight/obesity                | 484 | 60.0 (59.2, 60.9)     | (59.2, 60.9) |             |        |
| Smoking status                    |     |                       |              |             |        |
| Never smoker                      | 575 | 59.9 (59.0, 60.7)     | (59.0, 60.7) | 0.0137      |        |
| Ever smoker                       | 433 | 61.5 (60.5, 62.5)     | (60.5, 62.5) |             |        |
| Education level                   |     |                       |              |             |        |
| Less than college courses taken   | 245 | 62.3 (60.0, 63.6)     | (60.0, 63.6) | 0.0023      |        |
| College courses completed or more| 773 | 60.0 (59.2, 60.7)     | (59.2, 60.7) |             |        |

_t_ test analysis with statistical significance at _p_ < 0.05. ALS, amyotrophic lateral sclerosis. * Only women who answered the survey question were included in this analysis.
risk factors is displayed in Table 6. Female participants who entered menopause before age 50 had a mean ALS diagnosis age of 58.4 years while those entering menopause after age 50 had a mean diagnosis age of 64 years ($p < 0.0001$). Participants with menarche occurring at age 12 or later, who were never pregnant, or experienced their first pregnancy at or after age 30 all had a mean age at ALS diagnosis younger than their counterparts ($p = 0.0073$, 0.0002, and 0.0225, respectively). Female participants who were considered overweight or obese at age 40 were also diagnosed with ALS earlier than those with a BMI in the low or normal range ($p < 0.0001$). Ever smokers and women who did not attend college were more likely to be diagnosed with ALS earlier than their counterparts as well ($p = 0.0137$ and 0.0023, respectively). Among those who reported a family history of ALS or experienced a pregnancy after age 35 compared to those with no family history of ALS or no pregnancies after 35 years, there was no statistically significant difference in age of ALS diagnosis ($p = 0.1998$ and 0.5461, respectively).

**Discussion**

This study showed that women who completed menopause before age 50 were significantly more likely to be diagnosed with ALS before age 60 compared with those who completed menopause after age 50 which can be related to less endogenous estrogen exposure. Estradiol or estrogen is the primary female hormone and has been shown to regulate processes such as female reproductive and nonreproductive physiology [23]. The protective properties of estrogen in females are many and include preventing atherosclerosis, regulating a healthy immune response, and preventing osteoporosis by reducing bone resorption and increasing bone formation [24–28]. Estrogen has also been shown to possess neuroprotective properties in the areas of DNA repair and by lower levels of these chemicals [34]. This environmental factor could be a common cause of early menopause and ALS. Our present study did not examine circulating levels of persistent organic pollutants, but the role of environmental factors and how they affect ALS is an important research area [35].

In addition, women diagnosed before the age of 60 are more likely to have limb-onset than bulbar-onset ALS. More frequent bulbar-onset ALS, which was found at or after the age of 60, is consistent with other studies [36]. Cramps and fasciculations were also common with the registry cohort and are consistent with other studies as the leading early symptoms of ALS [37, 38]. It is unclear if site of onset and menopause are associated at this time. More research is needed to further explore this possible association.

This study is subject to several limitations. A major study limitation is that registrants self-select to participate in the web portal surveys. For example, ALS patients with internet access are presumably more likely to enroll via the web portal; this may skew the population of portal participants toward a younger, demographically white, and higher education status patient sample. The study population of participants with age <60 years (50.5%) is a larger proportion than what is seen in the National ALS Registry as a whole (31.1%) [2]. The portion of younger participants is overrepresented in this sample, and the oldest age group is underrepresented (Table 1) compared to the overall prevalence of persons living with ALS [2]. Additionally, racial diversity appears to be underrepresented in the sample with only 5.6% being nonwhite as compared to 12.1% in the registry as a whole [2, 39]. Potential reasons for these discrepancies might include lower access to computers that are required for self-registra-

Our findings from the National ALS Registry show women who completed menopause before the age of 50 are more likely to develop ALS before the age of 60. In the USA, the mean age of menopause is 51 [21]. These findings show that an earlier than average onset of menopause or a less endogenous estrogen exposure may play a role in the development of ALS in this cohort and require further investigation.

Other research has shown that women possessing high levels (>90th percentile) of persistent organic pollutants such as β-hexachlorocyclohexane, mirex, p,p’-DDE, 1,2,3,4,6,7,8-heptachlorodibenzofuran, mono-(2-ethyl-5-hydroxyhexyl) and mono-(2-ethyl-5-oxohexyl) phthalate, and polychlorinated biphenyl congeners −70, −99, −105, −118, −138, −153, −156, −170, and −183, which are considered to be endocrine-disrupting chemicals, had mean ages of menopause 1.9–3.8 years earlier than women with lower levels of these chemicals [34]. This environmental factor could be a common cause of early menopause and ALS. Further investigation is needed to role in the development of ALS in this cohort and require further investigation.
tion by residents of Western states, a region comprising a substantial nonwhite population [40]. Another possible study limitation is recall bias. Participants were asked to enter dates and ages from childhood through their ALS diagnosis as well as ALS symptoms before diagnosis. It is possible participants incorrectly estimated the date, ages, and symptoms resulting in possibly driving the odds toward null if the errors were random. Further, answering surveys is voluntary, and not everyone who registered took this survey.

**Conclusion**

ALS has a multifactorial disease etiology; therefore, it is not surprising that many unknowns still exist about this rare condition. The National ALS Registry is a multifaceted platform that advances research by evaluating potential risk factors, recruiting for national clinical trials and studies, funding research, and collecting as well as disseminating biospecimens and data nationally and internationally. The National ALS Registry reproductive history survey hosts over 1,000 participants on this topic.

The registry data presented here show a positive association between completing menopause before age 50 and earlier age at ALS diagnosis. Women in the National ALS Registry reporting menopause before age 50 were significantly more likely to be diagnosed with ALS before age 60 compared with those who reported completing menopause after age 50. This study is consistent with results of other reported research on smaller, less geographically diverse populations [32]. More research and a possible prospective study should be performed to clarify the association between endogenous estrogen exposure and ALS diagnosis in women. Environmental risk factors such as exposures to toxic substances may contribute to both ALS and earlier menopause. Better characterization of risk factors for ALS can assist clinicians in making referrals to an ALS specialist, resulting in earlier diagnosis, which could lead to earlier therapeutic interventions.

**Acknowledgment**

The authors are grateful to those living with ALS who give their valuable time to contribute important health data to researchers. Without their help, these findings, and countless others, would not be possible.

**Statement of Ethics**

The screening protocol used by ATSDR to collect data for this analysis was approved by the Centers for Disease Control and Prevention (CDC) Institutional Review Board.

**Conflict of Interest Statement**

The CDC/ATSDR authors have no declarations of interest. Dr. Pioro has no declarations of interest linked to the study.

**Funding Sources**

This project was designed, implemented, and funded by the federal government of the USA. The funder provided support in the form of salaries for authors J.R., P.M., T.L., and D.K.H.

**Author Contributions**

J.R., P.M., T.L., and D.K.H. assisted with study design, data collection and analysis, and preparation of the manuscript. E.P. assisted with data interpretation and preparation of the manuscript.

**Disclaimer**

The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry and should not be construed to represent any agency determination or policy.

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