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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Published by S. Karger AG, Basel

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 nonhereditary 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: $BMI = \text{weight (lb)} / [\text{height (in)}]^2 \times 703$ [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		<i>p</i> value
	<i>N</i> = 515	%	<i>N</i> = 503	%	
Diagnosis year					
Before 2014	107	20.8	69	13.7	0.0348
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	0.0145
Nonwhite	29	5.6	13	2.6	
BMI at registration					
Underweight/normal	187	36.6	226	45.2	0.0054
Overweight/obesity	324	63.4	274	54.8	
BMI at age 40					
Underweight/normal	206	43.4	284	56.9	<0.0001
Overweight/obesity	269	56.6	215	43.1	
Highest education					
Did not complete high school	17	3.3	33	6.5	0.0012
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	0.0925
Ever smoker	205	40.4	228	45.5	
Age at first menstrual cycle					
12 yr or older	177	37.1	265	54	0.454
<12 yr	300	62.9	226	46	
Age at menopause					
50 yr or older	158	35.4	297	54.2	<0.0001
<50 yr	288	64.6	251	45.8	
Ever pregnant					
Yes	440	85.5	454	90.3	0.046
No	74	14.5	49	9.7	
Pregnancies, <i>n</i>					
1	61	13.9	65	14.3	0.4857
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	0.0415
30 yr or older	90	20.4	69	15.2	
Age at last pregnancy					
<35 yr	351	79.6	363	80	0.8922
35 yr or older	90	20.4	91	20	
Family history of ALS					
Sporadic ALS	475	92.2	468	93	0.6214
Familial ALS	40	7.8	35	7	
χ ² analysis with statistical significance at <i>p</i> < 0.05. ALS, amyotrophic lateral sclerosis.					

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		<i>p</i> value
	<i>N</i> = 373	%	<i>N</i> = 382	%	<i>N</i> = 755	%	
Symptom onset site*							
Limb	284	76.1	227	59.4	511	67.7	<0.0001
Arm or hand	118	31.6	94	24.6	212	28.1	0.0317
Leg or foot	166	44.5	133	34.8	299	39.6	0.0065
Bulbar	75	20.1	138	36.1	213	28.2	<0.0001
Trunk/global	14	3.8	17	4.5	31	4.1	0.6295

χ^2 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.

around 60 years [15]. We analyzed diagnosis before age 60 versus at or after age 60. To see if correlations were greater, we shifted the age at diagnosis to analyze age at diagnosis before age 50 versus at or after that age. Finally, we also considered age at diagnosis as a continuous variable using the *t* test analyses to compare the mean age at diagnosis to several variables in the analysis. This was performed to determine if there was a significance difference in the age at diagnosis between samples. Because the typical site of onset differs between women and men, univariate analyses using χ^2 tests were performed to examine associations among site of onset (limb, bulbar, or trunk/global), as well as other symptoms experienced around an ALS diagnosis. Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for multivariate analysis. Backward elimination was used to establish the final reduced logistic regression model. Variables were included into the final model only if their *p* value was <0.05. The excluded variables did not meaningfully impact the magnitudes of the betas of variables retained in the final model. The models included race, education level, smoking history, BMI at the time the patient entered the registry and at age 40, family history of ALS, age at menarche, age at first pregnancy, number of pregnancies, and initial site of onset. Student's *t* test was used to examine differences in reporting of various risk factors and mean age of ALS diagnosis. All data analyses were performed using SAS 9.4 [22].

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 diag-

nosed 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		χ^2 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

χ^2 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 ^{`</sup>	OR <sup>`}	95% CI
Age at menopause ^a	0.6868	<0.0001	2.0	(1.5, 2.6)
Variable	Parameter estimate	p value [*]	OR [*]	95% CI
Age at menopause ^a	0.6064	<0.0001	1.8	(1.4, 2.4)
Age at first pregnancy ^b	0.4913	0.0091	1.6	(1.1, 2.4)
BMI at age 40 ^c	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 ^{`</sup>	OR <sup>`}	95% CI
Age at menopause ^a (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 ^a (ALS dx age <50)	3.8858	<0.0001	48.7	(11.8, 200.9)
Age at first pregnancy ^b	0.6797	0.0295	2.0	(1.1, 3.6)
BMI at age 40 ^c	0.6406	0.0129	1.9	(1.1, 3.1)
Education level ^d	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.

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

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, 2.4 $p = 0.0083$), whether a woman was ever pregnant (OR = 1.6, 95% CI = 1.04, 2.4, $p = 0.0339$), 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, never 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, is overweight or has obesity 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).

Treating age as a continuous variable, the mean age at ALS diagnosis within the study by various reproductive

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 being associated with increased risk and severity of Parkinson's disease and Alzheimer's disease [29–31].

The role of sex hormones in ALS is supported by studies showing that endogenous estrogen or progesterone appears to be protective against ALS triggers [32]. Previous studies have shown conflicting effects between exogenous estrogen and progesterone. Some studies have shown a decreased risk for ALS, and others show no association between postmenopausal use and the development of ALS [6, 33].

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. 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-registration; decreased awareness of the registry perhaps due to lower use of ALS specialty clinics; and reduced participa-

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.

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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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