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Reproductive history and age of onset for women diagnosed with amyotrophic lateral sclerosis (ALS), Data from the National ALS Registry: 2010 – 2018

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurological disease of largely unknown etiology with no cure. The National ALS Registry (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 age >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, body mass index (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 non-white (p=0.015), had attended college (p=0.0012), had an 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).

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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.

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.

Keywords

Amyotrophic lateral sclerosis; motor neuron disease; females; menopause; reproductive history

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 United States (US) over 16,000, or 5.2/100,000 people, lived with ALS in 2016 [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 non-heredity 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 as well as 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 have 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 United States (U.S.) participants enrolled in the National ALS Registry (Registry). The Registry is the largest population registry for ALS in the U.S. [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 U.S. 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 (Registry) to help clarify the epidemiology of ALS in the U.S. [11]. While details about the Registry's objectives are presented elsewhere [2], briefly,

the Registry's purpose is to quantify the incidence and prevalence of ALS in the U.S., 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 de-duplicated to ensure that individuals are not counted twice. To verify ALS status within the web portal, ATSDR adopted the six questions from the U.S. 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, pre-diagnosis symptoms, and female reproductive history. Currently, there are 17 survey modules available shown in Supplementary Table 1 [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 towards 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 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 Supplementary 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, the most recent year data were available.

Data Analysis

Selected demographic characteristics including race, age at diagnosis, body mass index, 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 non-white. If more than one race was selected, participants were categorized as non-white. Body mass index (BMI) was calculated using the standard formula: BMI = weight (lb) / [height (in)]^2 x 703 [20]. In the United States the mean age of menopause is 51 [21], so the main predictor variable for this analysis was age at menopause (less than 50 years 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 around 60 years [15]. We analyzed diagnosis before age 60 vs. 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 vs. at or after that age. Lastly, we also considered age at diagnosis as a continuous variable using 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 typical site of onset differs between women and men, univariate analyses using chi-square 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 analysis was 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 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 (less than 60 years versus at or greater than 60 years) are 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 odds ratio 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 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 less than 50 years, from 60 years, increased the crude odds ratio 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), other adjustments were not statistically significant. The three 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, p=0.0002, and p=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 p=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 p=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 non-reproductive 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 appear 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 showing 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 United States 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 (POPs) 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, 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 to 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 POPs, 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 less than 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 participation by residents of western states, a region comprising a substantial non-white 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 towards the 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 multi-faceted 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics among US women with ALS who responded to the National ALS Registry's Hormonal and Reproductive History Survey (October 19, 2010–December 31, 2018)

Characteristic	Diagnosis age < 60 years		Diagnosis age ≥ 60 years		p-value
	N = 515	%	N = 503	%	
Diagnosis Year					0.0348
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					0.0145
White	486	94.4	490	97.4	
Non-white	29	5.6	13	2.6	
BMI at Registration					0.0054
Underweight/Normal	187	36.6	226	45.2	
Overweight/Obesity	324	63.4	274	54.8	
BMI at Age 40					<0.0001
Underweight/Normal	206	43.4	284	56.9	
Overweight/Obesity	269	56.6	215	43.1	
Highest Education					0.0012
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%	
Post graduate degree	93	18.1%	99	19.6%	
Smoking Status					0.0925
Never smoker	303	59.6%	272	54.3%	
Ever smoker	205	40.4%	228	45.5%	
Age at first menustral cycle					0.454
12 years or older	177	37.1	265	54	
Less than 12 years	300	62.9	226	46	
Age at Menopause					<0.0001
50 years or older	158	35.4	297	54.2	
Less than 50 years	288	64.6	251	45.8	
Ever Pregnant					0.046
Yes	440	85.5	454	90.3	
No	74	14.5	49	9.7	

Characteristic	Diagnosis age < 60 years		Diagnosis age ≥ 60 years		p-value
	N = 515	%	N = 503	%	
Number of pregnancies					0.4857
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					0.0415
Less than 30 years	351	79.6	385	84.8	
30 years or older	90	20.4	69	15.2	
Age at last pregnancy					0.8922
Less than 35 years	351	79.6	363	80	
35 years or older	90	20.4	91	20	
Family History of ALS					0.6214
Sporadic ALS	475	92.2	468	93	
Familial ALS	40	7.8	35	7	

Chi square analysis with statistical significance at $p<0.05$.

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–December 31, 2018)

Characteristic	Diagnosis age < 60 years		Diagnosis age ≥ 60 years		Total		p-value
	N = 373	%	N = 382	%	N = 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

*Initial site of onset refers to the first body region where a patient reported a weakness or symptom prior to ALS diagnosis.

Chi square analysis with statistical significance at $p<0.05$.

Table 3.

Other Symptoms Experienced among 1,018 US women with ALS who responded to the National ALS ALS Registry's Hormonal and Reproductive History Survey (October 19, 2010–December 31, 2018)

Other Symptoms	Diagnosis age < 60 years		Diagnosis age ≥ 60 years		Total		Chi-square p-value
(Have you ever experienced the following?)	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	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	57	15	116	15.5	0.8881

Chi square analysis, statistically significant at $p<0.05$.

Table 4.

Logistic Regression Analyses for an ALS Diagnosis before age 60 for Women, October 19, 2010 - December 31, 2018

Variable	Parameter Estimate	p-value`	OR`	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)

` - 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

GEE analysis with significance at $p<0.05$

Table 5.

Logistic Regression Analyses for an ALS Diagnosis before age 50 for Women, October 19, 2010 - December 31, 2018

Variable	Parameter Estimate	p-value`	OR`	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)

` - 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

GEE analysis with significance at p<0.05

Table 6.

Mean Age at Diagnosis by reproductive risk factors, among US women* with ALS who responded to the National ALS ALS Registry's Hormonal and Reproductive History Survey (October 19, 2010–December 31, 2018)

Variable	N	Mean Age of Diagnosis	95% CI	Pooled Pr > |t|
Menopause				<0.0001
< 50 years old	526	58.4	(57.4, 59.4)	
≥ 50 years old	442	64	(63.4, 64.7)	
Age at menstration				0.0073
< 12 years old	181	61.8	(60.2, 63.3)	
≥ 12 years old	837	60.2	(59.5, 61.0)	
Ever pregnant				0.0002
Yes	894	61	(60.3, 61.7)	
No	123	57.2	(55.2, 59.3)	
Age at first pregnancy				0.0029
< 30 years old	736	61.4	(60.7, 62.2)	
≥ 30 years old	159	58.8	(57.2, 60.3)	
Age at last pregnancy				0.9693
< 35 years old	714	61	(60.2, 61.7)	
≥ 35 years old	181	60.9	(59.5, 62.4)	
Family History of ALS				0.1998
No	943	60.6	(60.0, 61.3)	
Yes	75	59	(56.4, 61.6)	
BMI at age 40				<0.0001
Underweight/Normal	490	62.9	(62.1, 63.7)	
Overweight/Obesity	484	60	(59.2, 60.9)	
Smoking Status				0.0137
Never smoker	575	59.9	(59.0, 60.7)	
Ever smoker	433	61.5	(60.5, 62.5)	
Education Level				0.0023
Less than college courses taken	245	62.3	(61.0, 63.6)	
College courses completed or more	773	60.0	(59.2, 60.7)	

*Only women who answered the survey question were included in this analysis.

T-test analysis with statistical significance at $p<0.05$.