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Impact of environmental and lifestyle factors on progression and survival in a large Chinese amyotrophic lateral sclerosis cohort

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Abstract

Objective: To investigate the impacts of environmental and lifestyle factors on progression and survival in a large Chinese amyotrophic lateral sclerosis (ALS) cohort. *Methods:* We investigated a cohort of 1,312 sALS patients prospectively. A questionnaire was designed to collect information on environmental exposure and lifestyle at baseline. Uni- and multivariate analysis were performed to analyze the influence of environmental and lifestyle factors on the onset age, bulbar onset, progression rate and survival time of ALS. *Results:* A total of 1,050 questionnaires were finally received from the patients, among which 407 questionnaires were fully filled out. Low educational level and ever smoked were significantly related to late onset in both univariate and multivariate analysis with backward section ($p<0.05$). Exposure to organophosphorus pesticide was significantly related to bulbar onset ($p=0.027$) and rapid progression ($p=0.007$). Ever drinking alcohol was related to longer survival time in Cox regression model ($p=0.040$) and the mean survival time of non-drinkers was significantly higher than patients with history of drinking alcohol ($p=0.023$).
Conclusion: In Chinese ALS population, low educational level was an independent indicator of late onset. Exposure to organophosphorus pesticide was the risk factor for bulbar onset and rapid progression. Smoking and drinking alcohol were less common among ALS patients with late onset and long survival time.

Keywords: Environmental exposure, lifestyle, amyotrophic lateral sclerosis

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease, characterized by involvement of both upper and lower motor neuron (UMN and LMN).[1] The relentless decline in functional status and lack of effective treatment cause great suffering to ALS patients and their caregivers, which have received the attention of investigators worldwide. Incidence rate for ALS varies from different regions, range between 0.8 and 4.7 per 100,000 person-years.[2,3] Despite its rarity, it was reported that there was an increasing trend of both incidence and mortality rates of ALS over the recent decades.[3] Specific environmental exposure and lifestyle may be part of the causes.

Increasing epidemiological studies suggested the risk factors of early ALS onset, such as previous exposure to heavy metals and pesticides[4,5], history of physical trauma/injury (including head trauma/injury) and military experience[6], smoking[7], and others. Some of them have been confirmed to be involved in the pathogenesis of ALS by evidence-based studies[8] and basic experiments.[9] In recent years, the management of ALS has shifted from an attitude of nihilism to treatments that prolonged survival and offered hope. Identification of risk factors for poor prognosis is of great significance for the comprehensive management of ALS patients.

To the best of our knowledge, studies on impacts of environmental and lifestyle factors on ALS progression and survival in Chinese population are scarce. Therefore, we investigated a large population of Chinese sporadic ALS

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(sALS) patients to further elucidate the underlying prognostic factors of ALS. We hope to provide guidance for lifestyle changes in ALS patients through the study.

METHODS

Subjects

A prospective single-center cohort study was conducted at the Department of Neurology, Peking Union Medical College Hospital (PUMCH). Suspected ALS patients were recruited and registered online if they fulfilled the criteria: 1) progressive weakness or atrophy in limbs or progressive bulbar dysfunction, such as dysphagia, hoarseness; 2) no electrophysiological evidence for sensory abnormalities that could not be explained by other causes; 3) ancillary examinations excluding other causes. A total of 2551 patients were consecutively assessed in this study between January 2014 and October 2023. All enrolled patients were recorded with their name, gender, age and clinical symptoms with detailed physical examination. All included patients were assessed using the ALS Functional Rating Scale-Revised (ALSFRS-R).[10] Muscle strength was measured using the Medical Research Council (MRC) score, including bilateral assessment of the following limb muscle actions: shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, finger flexion, finger extension, thumb abduction, little finger abduction, hip flexion, knee flexion, knee extension, ankle dorsal extension, ankle plantar flexion, toe dorsal extension, and toe plantar flexion. The total MRC score was 160.

A follow-up interview was performed every three months either by phone call or in our outpatient clinic to collect a follow-up ALSFRS-R score. Two experienced clinicians (Lei Zhang and Jianfeng Ding) completed the assessment of ALSFRS-R independently, and disagreements were resolved by consensus. Patients that could not be followed up at the appointed time were excluded from our analysis. As shown in Figure 1, 2453 patients completed the follow-up for at least 6 months and 56 patients were excluded due to misdiagnosis. In the year to October 2023, a total of 1,911 patients were diagnosed as definite or probable ALS according to the revised El Escorial criteria.[11] Among them, 688 patients died or needed invasive respiratory support during follow-up. Patients with family history of ALS or regular intake of riluzole were excluded from analysis.

The progression rate was calculated by the difference of the ALSFRS-R score at the first and

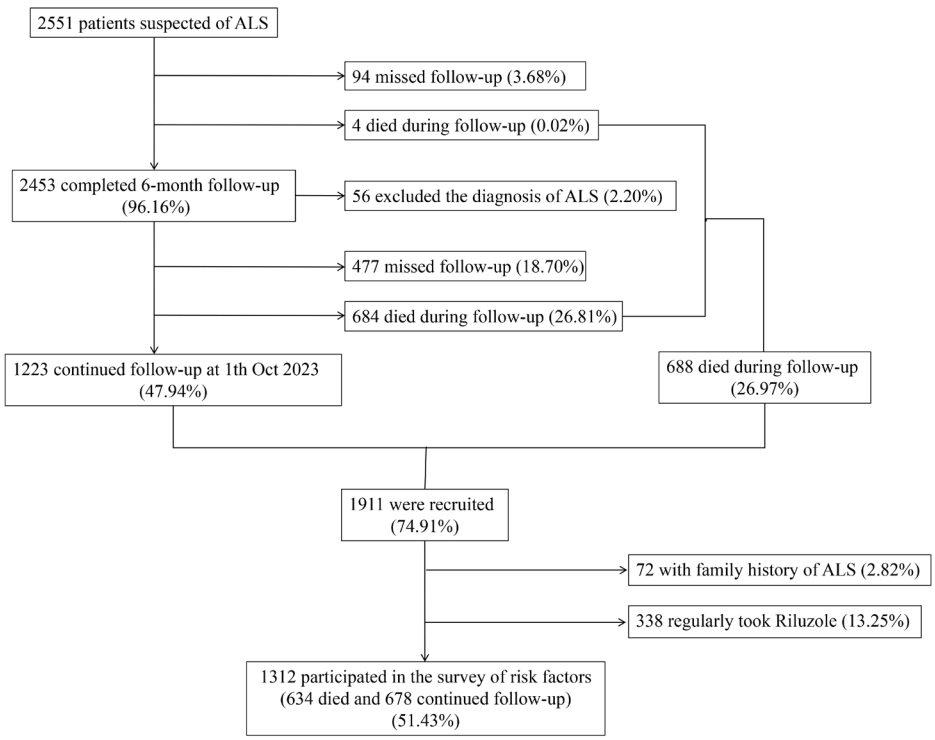

Figure 1. The flowchart of patient screening

last visit divided by the time interval between these two visits in months (decrease of ALSFRS-R per month).[12] Survival time referred to the time (months) between onset of ALS and death or need for invasive respiratory support.

This study was approved by the Ethics Committee of the PUMCH (JS1218). All enrolled patients provided written, informed consent to be included in the study.

Survey on environmental and lifestyle factors

We designed a questionnaire to investigate potential risk factors for ALS progression and survival. As shown in Supplementary Table 1, a total of 16 items were involved in the questionnaire. All items were determined by two senior authors (Mingsheng Liu and Liying Cui) based pm the current literature on ALS. Each patient voluntarily chose whether to participate in the survey at recruitment. Patients who were willing to fill out the questionnaire were asked to answer every question as truthfully as possible. The authors (Nan Hu and Ming Qi) would offer help to patients who had difficulty in handwriting or did not understand the items in the questionnaire.

In the study, different types of smoking status were classified by the smoking period and the quantity of tobacco the patients smoke/smoked each day. Heavy smokers were patient who started smoking early, reached their maximum level (no less than 2 packs per day) before onset of ALS and never quit smoking. Occasional smokers were patient who started smoking early, reached their maximum level (less than 2 packs per day) before onset of ALS and never quit smoking. Ever smokers were those who ever smoked but quit smoking before onset of ALS. Similarly, drinking status was classified based on the drinking frequency and the average amount of alcohol consumed (g) per day (The Finnish Current Care Guideline 2011) (pure alcohol): occasional drinking (women < 24 g/day; men < 48 g/day; < 4 times/week), heavy drinking (women ≥24 g/day; men ≥48 g/day; ≥4times/week) and ever drinking (quit drinking before onset of ALS). According to the conditions of China, we identified education experience of no less than 11 years as high education level.

Statistical analysis

The Shapiro-Wilk test was used to assess whether data exhibited a normal distribution. Normally distributed variables including age were expressed as means (standard deviation, SD). One-way analysis of variance (ANOVA) was used to compare the mean value of studied variables among different subgroups.

Four indicators that attracted great attention from clinicians were selected as the outcome indicators in the study: onset age, bulbar onset, progression rate and survival time.

To analyze the influence of included factors on onset age, bulbar onset and progression rate of ALS, we performed linear/logistic regression with ALSFRS-R decrease per month and survival time as the dependent variables and environmental or lifestyle factor as the independent one. We first analyzed each variable in a univariate regression with Bonferroni correction. Afterwards, variables with a low p value ($p<0.2$) were included in a multivariate regression analysis. Using backward selection, relevant factors ($p<0.05$, significance) were finally identified.

Kaplan-Meier curve was used for survival analysis, with ALS onset as zero time and death as the end-point event. Log-rank tests were applied to analyze the impacts of included factors on survival time. A multivariate regression analysis (Cox proportional hazard regression model) which included all the variables with $p<0.2$ in the univariate model, was used to assess the independent influence of each variable on survival.

It is worth noting that basic variables and confounding factors as age, gender, onset region, and body mass index (BMI) were included in the multivariate analysis of ALS progression and survival time (data were not provided).

Statistical analyses were performed using SPSS 23.0.

RESULTS

Characteristics of 1,312 ALS patients that participated in the questionnaire were provided in Supplementary Table 1. Six hundred and thirty-eight patients died, and thirty patients needed invasive respiratory support during follow-up. Among them, 204 (29.65%) died of respiratory failure. Kaplan-Meier analysis showed that the median survival time was 54.00 (95%CI: 48.58-59.32) months (Figure 2).

Finally, we received 1,050 (80.03%) questionnaires from the patients. Due to the large number of blanks in the collected questionnaires, we first conducted univariate regression or survival analysis for each indicator in order to make the most of the data. Then, patients that completed all the items in the questionnaire (407 (31.02%)

Table 1: Impacts of environmental and lifestyle factors on ALS
Part I Univariate regression/Binary logistic regression/Log rank test with Bonferroni correction

Factors	N#	Onset age	Bulbar onset	Progression rate	Survival time
Urban (or rural) residence	738	0.288	0.169	0.803	**0.033**
High education level	682	**0.022**	0.313	0.075	0.098
Married	740	**<0.001**	0.477	0.065	0.678
Academic occupation	903	0.064	0.638	**0.008**	**0.001**
Military service	832	0.376	0.172	0.307	0.806
Head trauma	946	0.409	0.862	0.419	0.844
Other trauma	724	0.443	0.389	0.713	0.060
CO poisoning	987	0.719	0.721	0.957	0.296
Surgery	991	0.907	0.108	0.467	0.197
General anesthesia		0.836	0.847	0.412	0.495
Smoking	987	0.483	0.092	0.856	0.425
Heavy		0.403	0.260	0.509	**0.002**
Occasional		0.174	0.152	0.377	**0.023**
Ever		**0.001**	0.956	0.499	**0.023**
Drinking	983	0.707	**0.011**	0.956	0.693
Heavy		0.223	0.782	0.957	0.156
Occasional		0.660	**0.026**	0.332	**<0.001**
Ever		0.423	0.090	0.662	**0.018**
Hair dyeing	1003	0.793	0.453	0.939	0.688
Pet raising	974	0.730	0.753	0.506	0.414
Organophosphorus pesticide	1012	0.073	**0.029**	0.089	**0.030**
Other organic solvents	832	0.441	0.361	0.695	0.181
Heavy metal	830	0.683	0.885	0.930	0.974
Intensive exercise	789	0.581	0.850	0.300	0.425

Note: Significant data (P<0.05) were bold.
Number of available data.

Part II Multivariate regression/Multiple logistic regression/Cox regression analysis (N*=407)

Factors	Onset age		Bulbar onset		Progression rate		Survival time
	Multi-variate	Backward selection	Multi-variate	Backward selection	Multi-variate	Backward selection	Cox
Urban (or rural) residence			0.233				
High education level	**0.017**	**0.015**			0.120		0.214
Married	0.237						
Academia occupation					0.268		0.195
Other trauma							0.051
Smoking							
Heavy							
Occasional							0.053
Ever	**0.003**	**0.003**					0.055
Drinking			0.051				
Heavy							
Occasional			0.131				
Ever			0.248				**0.040**
Organophosphorus pesticide			**0.039**	**0.027**	**0.010**	**0.007**	0.102
Other organic solvents							0.265

Note: Significant data (P<0.05) were bold.
*Number of patients involving in multivariate analysis.
Abbreviations: ALS amyotrophic lateral sclerosis.

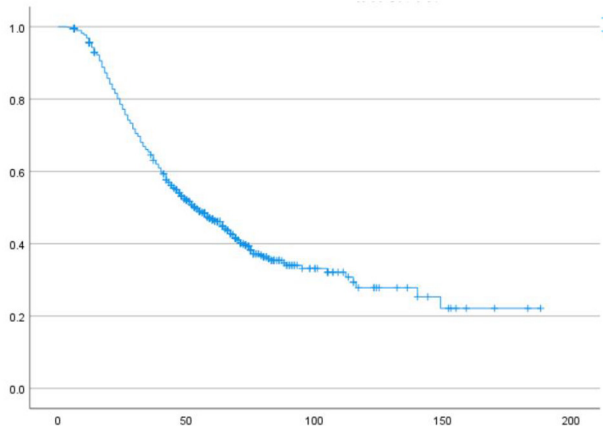

Figure 2. Kaplan-Meier curve representing survival of ALS patients. ×-axis: time in months; y-axis: percentage of survived patients.

were reanalyzed using univariate analysis (data were not presented) and variables with p<0.2 were further included in multivariate analysis. It was noteworthy that there was no significant difference in onset age, bulbar onset (%), progression rate or survival time between patients who completed and did not complete the questionnaire (p>0.05).

Onset age

As shown in Table 1, low educational level was significantly related to late onset in both univariate (p=0.022) and multivariate analysis with backward section (p=0.015). Marital status was statistically correlated to early onset in univariate analysis (p<0.001), which were not significant in multivariate regression (p=0.237).

Ever smoking was an independent factor of late onset (p=0.003), while there was no significant difference in onset age between ALS smokers and non-smokers (p=0.483). Comparisons in onset age indicated no significant difference among patients with varying degrees of smoking (p=0.106) (Figure 3).

Bulbar onset

Univariate logistic analysis showed that drinking (p=0.011) and exposure to organophosphorus pesticide (p=0.029) were risk factors of bulbar onset. Multivariate analysis showed that only exposure to organophosphorus pesticide was positively related to bulbar onset after backward selection (p=0.027). (Table 1 and Figure 3)

Progression rate

Among included factors, only academic occupation was remarkably related to low progression rate in univariate regression (p=0.008). Multivariate analysis suggested that exposure to organophosphorus pesticide was a risk factor for rapid progression (p=0.007).

Survival time

Log rank test revealed urban residence (p=0.033) and academic occupation (0.001) were prominently related to the long survival time of ALS, while heavy/occasional/ever smoking (p<0.05), occasional/ever drinking (p<0.05) and exposure to organophosphorus pesticide (p=0.030) were indicators of short survival time. Among them, only the relationship between ever drinking remained significant in Cox regression model (p=0.040). Further analysis showed that the mean survival time of non-drinkers was significantly higher than patients with history of drinking (p=0.023) (Figure 3).

DISCUSSION

Increasing studies have been done to explore the potential risk factors of ALS, hoping to provide new insights for the pathogenesis of ALS and guidance on lifestyle for ALS population. In the study, we designed a self-report questionnaire to further investigate the impact of environmental and lifestyle factors on ALS course and prognosis.

Our results revealed three possible factors that might influence the onset of age among ALS patients, among which low educational level was an independent indicator of late onset in multivariate analysis. Inconsistent with our results, Sutedja *et al*. reported that an increased

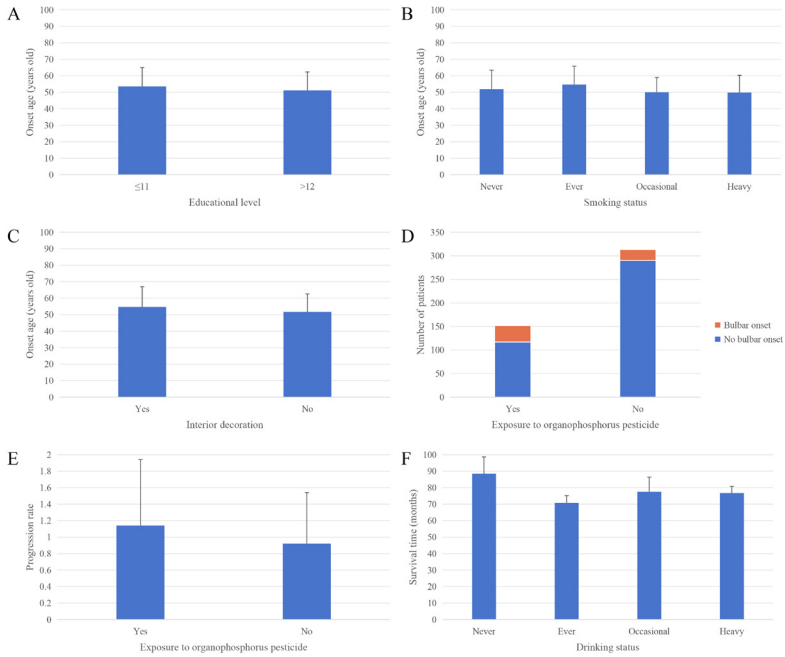

Figure 3. Results of significant data in multivariate regression/multiple logistic regression/Cox regression analysis.

risk of developing ALS among people with a low level of education[13] while no other studies suggested the significant relationship between educational level and ALS risk.[14,15] We believed that patients with high educational level might pay more attention to their physical health, thus being easier to detect mild limb weakness in the early stages. Married status possibly influences the onset age of ALS patients through changes in their other lifestyles, which did not affect the onset of ALS itself. Smoking has previously been believed to correlate to ALS risk[7,16], possibly due to the neuronal damage from nitric oxide or other components of cigarette smoke.[17] Our results showed a slightly higher onset age among ALS patients with never smoking or ever smoking than those with heavy or occasional smoking, but no significant difference was revealed. One quantitative indicator involving the amount and frequency of smoking per day, and the total years of smoking might further elucidate the relationship between smoking and ALS risk, which deserved future studies. Based on the current results, we recommended that ALS patients should not smoke or quit smoking as early as possible for the benefit of their health.

Bulbar onset has been identified as one independent factor of rapid progression and poor prognosis of ALS.[18] Therefore, we investigated potential risk factors of bulbar onset in our cohort. Multivariate analysis suggested exposure to organophosphorus pesticide might increase the risk of bulbar onset. Drinking might act as a confounding factor rather than a independent factor of bulbar onset. Furby *et al*. reported that bulbar forms of onset more prevailed among agricultural workers as compared with other occupations, which might be attributed to exposure to agricultural chemicals or contact with animals linked to agricultural work.[19] The underlying mechanisms remained unclear, which needed further investigations.

For patients diagnosed with ALS, more concern might be paid on progression rate and survival time. Among included indicators, only academic occupation and exposure to organophosphorus pesticide showed significant relationship with progression rate. The correlation between occupation and ALS course might be the epiphenomenon of impact of income level, physical activity, health care and underlying environmental exposure on ALS. Experimental studies have reported that organophosphorus pesticide might cause cholinergic deficit and elevated oxidative stress or act on epigenetic modifications[20], which could accelerate the degeneration of neurons and resulted in rapid loss of voluntary function. Therefore, exposure to pesticides should be avoided in ALS patients.

As for survival time, we found only abstaining from alcohol was independently related to long survival time. Subgroup analysis showed the mean

survival time of non-drinkers was significantly longer than patients with history of drinking. The impact of alcohol on the nervous system remained unclear, and a meta-analysis in 2012 indicated an inverse association between alcohol consumption and ALS, suggesting alcohol might be a protective factor against ALS.[21] Besides, in vivo experiments carried out in a transgenic mouse model for ALS showed that mice fed lyophilized red wine had significantly increased survival as compared with untreated control animals, possibly because of antioxidant effects or reduced glutamate-induced apoptosis.[22,23] All these seemed to be inconsistent with our results, which might be attributed to the types of wine. Also, given that most studies were from Western cohorts, genetic diversity might be involved in some of the differences, which could result in differences in the metabolism of alcohol between ethnic groups. Based on our results, drinking should be totally avoided among ALS patients.

In addition to the factors we discussed above, there were many other factors that might affect the course of ALS, such as income level, health care and medical support, and others. These factors might cause significant influences in our results and deserved further investigations. Besides, due to the missing data, there were differences in the population included in univariate and multivariate analyses, which might result in selection biases. Besides, as our data were self-reported by patients, bias in memory could not be neglected in the interpretation of the results. Future studies should aim at providing incredible and prospective data on the environmental exposure and lifestyle among ALS, and try to establish a predictive questionnaire for the progression rate and survival time among ALS population.

In conclusion, among Chinese ALS population, low educational level was an independent indicator of late onset. Exposure to organophosphorus pesticide was the risk factor for bulbar onset and rapid progression. Smoking and drinking were less common among ALS patients with late onset and long survival time.

DISCLOSURE

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Conflict of interest: None

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Supplementary Table 1. Characterization of ALS cohort at baseline

Characterization	ALS patients (n=1312)
Age of onset (years)	53.21±10.88
Gender (male/female)	713/599
BMI (kg/m^2)	23.20±3.14
Nationality (N, %)	
Han	1278 (97.41%)
Hui	13 (0.99%)
Manchu	12 (0.91%)
Mongolian	5 (0.38%)
Uygur	3 (0.23%)
Zhuang	1 (0.08%)
Disease duration (months)	17.91±16.58
Side of onset (N, %)	
Bulbar	314 (23.93%)
Upper limb	370 (28.21%)
Lower limb	444 (33.84%)
Multiple	184 (14.02%)
Total MRC	130.81±23.84
ALSFRS-R	38.09±6.68

Abbreviations: ALS amyotrophic lateral sclerosis; ALSFRS-R the ALS Functional Rating Scale-Revised; BMI body mass index; MRC the Medical Research Council; SD standard deviation.
Note: Data were presented as mean±SD.

Supplementary Table 2. Questionnaire on environmental and lifestyle factors among ALS patients.
Preface: Dear patients, this is a questionnaire initiated by the Department of Neurology at Peking Union Medical College Hospital (PUMCH) regarding the specific environmental factors and lifestyle of ALS (anyotrophic lateral sclerosis) patients. The survey is completely voluntary, and you can choose to participate or not to participate. We would greatly appreciate it if you could finish the questionnaire and we guarantee that any information you provide is for research purposes only. It is noteworthy that all answers should be based on facts and you are free to leave the question(s) beyond recall blank. The whole survey will take you around 10 minutes.

Name:	Gender:	Age:
Patient ID:	Date of filling:	
1. Your long-term residence:		
2. Your educational background: (Time of education: years)		
3. Your marital status • Married and not divorced (Date of marriage:) • Married but divorced (Date of marriage: ;Date of divorce:) • Unmarried		
4. Your work experience (If you have several work experiences, please list and provide the corresponding periods separately): 1) (From to) 2) (From to)		
5. Did you have military service? • Yes Services: Army (Time: years) Navy (Time: years) Air (Time: years) Others (Time: years) • No		
6. Did you get your head injured? • Yes (Data: ; Location:) • Never		
7. Do you have a history of other trauma (except for head trauma)? • Yes (Date: ;Location:) • Never		
8. Do you have a history of carbon monoxide poisoning (gas poisoning)? • Yes (Date:) • Never		
9. Do you have a history of surgery? • Yes (Date: ; Location: ; General anesthesia: Yes/No) • Never		
10. Do you smoke? • Yes (Age starting smoking: ; packs/day on average) Have you quit smoking? 1) Yes (Age quit smoking:); 2) No • Never		

11. Do you drink alcohol? • Yes (Age starting drinking: ; Daily alcohol consumption: g; The main kind of alcohol: Red wine/Write wine/Beer; Frequency of drinking: <4 times/week≥4times/week) Have you quit drinking? 2) Yes (Age quit smoking:); 2) No • Never
12. Did you dye your hair? • Yes (times/year) • Never
13. Do you raise pets? • Yes (Species:) • Never
14. Do you have exposure to organophosphorus pesticides or other types of organic solvents? • Yes (Types of organic solvents: ; How many years:) • Never
15. Do you have exposure to heavy metals (e.g. mercury, lead, etc)? • Yes (How many years:) • Never
16. Do you have regular and intensive exercise? • Yes (times/months); • No