



## Short communication

## Earlier age of onset in multiple system atrophy with smoking and heavy alcohol use

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## ABSTRACT

**Objective:** To determine whether smoking or alcohol use impacts the age of onset and disease duration in multiple system atrophy (MSA).

**Methods:** All patients diagnosed with MSA at Mayo Clinic, Rochester between 1998 and 2012 completed standardized questionnaires surveying smoking and alcohol use at the time of presentation.

**Results:** Of 551 patients with smoking and alcohol use data, 281 were past or present smokers with age of onset of 60.76 years compared to 62.97 years in controls ( $p = 0.0144$ ). Age of onset in the 87 heavy alcohol users was 56.87 years compared to 62.97 years in controls ( $p = 0.0133$ ). There was no difference in disease duration for smokers ( $p = 0.2758$ ) or heavy alcohol users ( $p = 0.4820$ ) compared to controls.

**Conclusion:** Our findings show that smoking history and/or heavy alcohol use is associated with younger age of onset in MSA but do not influence survival.

## 1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic failure with parkinsonism (MSA-P) and/or cerebellar ataxia (MSA-C) [1]. While various prognostic factors predict shortened survival in MSA, data regarding modifiable risk factors in MSA have shown mixed results [2]. Epidemiologic studies are conflicting on whether alcohol use reduces the risk of developing MSA [3,4] while studies on smoking and risk of MSA have also demonstrated mixed results [5,6].

We sought to investigate the relationship between smoking and alcohol use on age of onset and survival in MSA from a large cohort of patients with prospectively collected information regarding smoking and alcohol habits. We hypothesized that smoking would delay development of symptoms in MSA based on the accepted inverse association between Parkinson disease and smoking [7,8]. Additionally, we hypothesized that alcohol use would be associated with earlier age of onset in MSA due to toxic effects on the cerebellum from alcohol leading to earlier manifestation of symptoms.

## 2. Methods

## 2.1. Study design

This study was approved by the Mayo Clinic Institutional Review Board. All included patients had signed a general informed consent form allowing their medical records to be used for research purposes. All patients diagnosed with MSA at Mayo Clinic, Rochester, MN between January 1998 and December 2012 with autonomic function testing were evaluated. All patients were asked to complete standardized medical and social history forms documenting their own personal smoking (current and past use) and alcohol (current and past use with alcohol abuse screening questions) use at time of the neurologic consultation. Results from patient-reported questionnaire were correlated with physician documentation regarding smoking and alcohol use in the medical record. Patients were categorized as probable or possible MSA based on consensus criteria and classified as MSA-P or C based on predominant symptom complex upon initial evaluation [1]. MSA symptom onset was recorded from clinical notes that documented the patient's first reported symptom, which could include motor or autonomic symptoms. Survival and death data was recorded from the clinical record and social security database. Patients were divided into

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groups based on their response to questions related to smoking and alcohol use. The control group included all MSA patients who had neither current or past smoking nor heavy alcohol use history.

## 2.2. Smoking

Patients reported whether they were current or past smokers, and if so, estimated the number of packs per day and number of years of smoking. Past or current smokers were included in the smoking group.

## 2.3. Alcohol

Patients reported whether they ever used alcohol or not, and if so, estimated their average weekly number of drinks. Respondents were queried whether or not they ever felt the need to cut back, or if they abused alcohol. According to the 2015–2020 dietary guidelines for Americans, moderate alcohol use is considered 1 alcoholic unit per day for women, and 2 alcoholic units for men [9]. For the current study, participants reporting consumption of  $\geq 14$  units per week (regardless of gender) were classified as heavy alcohol users. If patients reported a history of alcohol abuse or the need to cut back, they were classified as heavy alcohol users.

## 2.4. Statistical analysis

SAS and JMP statistical software were used to perform statistical analyses, with statistical significance set at  $p < 0.05$ . Categorical data was analyzed using  $\chi^2$  testing; continuous variables analyzed using the Student's *t*-test. A linear regression model evaluated relationships between smoking and heavy alcohol use and age of symptom onset. Censored Kaplan-Meier estimates with survival curves were used to assess probability of disease onset at different ages by smoking and heavy alcohol use groups.

## 2.5. Data availability statement

Anonymized data will be shared by request to any qualified investigator.

## 3. Results

### 3.1. Demographics

Of 685 patients with MSA, 594 had probable MSA (87%), and 91 had possible MSA (13%). Of those patients, 551 patients had complete smoking and alcohol data. 134 patients did not complete the questionnaires and were not included in the analysis. In the cohort, 36 patients had autopsy which confirmed MSA diagnosis in all 36 patients.

Smoking history was reported in 281 (51%) patients with 215 of these 281 (39%) patients having no history of heavy alcohol use. Of patients with smoking history, 186 had pack year data with a median pack year of 22.5 (interquartile range 10–40). History of heavy alcohol use was reported in 87 (16%) patients, 21 (4%) with no associated smoking history. Both smoking and heavy alcohol history was reported in 66 (12%) patients. The MSA control group contained 249 (45%) patients (Table 1).

Both smoking and heavy alcohol use was more common in males (Table 1). There was no difference in age of onset between males and females ( $p = 0.3661$ ). Clinically, the groups appeared similar other than an increased frequency of orthostatic intolerance in patients with both smoking and associated heavy alcohol use history. Ataxia was more common in patients with heavy alcohol use regardless of smoking status while parkinsonism was less common in patients with both smoking and heavy alcohol use (Table 1).

### 3.2. MSA patients with smoking history have younger age of onset

Age of onset in the 281 past or present smokers was 60.76 years compared to 62.97 years in the control group ( $p = 0.0144$ ) (Fig. 1). There was no difference in disease duration ( $p = 0.2758$ ) based on smoking history (Table 1).

### 3.3. MSA patients with history of heavy alcohol use have younger age of onset

Age of onset in the 87 heavy alcohol users was 56.87 years compared to 62.97 years in controls ( $p = 0.0133$ ) (Fig. 1). There was no difference in disease duration ( $p = 0.4820$ ) between heavy alcohol users and no heavy alcohol use (Table 1).

### 3.4. Combined group comparison

Using a linear regression model, there was no significant interaction between smoking and alcohol ( $p = 0.0974$ ). In the multivariate model, MSA patients with a smoking history had age of onset 1.67 years earlier compared to a never smokers ( $p = 0.0469$ ) and MSA patients with heavy alcohol use history had age of onset 2.6 years earlier compared to non-heavy alcohol users ( $p = 0.0239$ ). Therefore, it may be inferred that an MSA patient who has both a history of smoking and heavy alcohol use has a 4.3 year earlier age of onset compared to an MSA patient with no history of smoking or heavy alcohol use.

## 4. Discussion

MSA patients with smoking and/or heavy alcohol use history had earlier age of onset compared to controls with no history of smoking or heavy alcohol use. The difference in age of onset of 4.3 years with both smoking and heavy alcohol use history is considerable and while smoking and heavy alcohol use often coexist, the effect on age of onset in MSA appears to be independent. While this study design does not seek to show causation, these findings represent a potential modifiable risk factor for earlier development of MSA which is notable with the current lack of disease-modifying treatments. Additionally, we found no difference in survival based on smoking and/or alcohol use history. Therefore, smoking and heavy alcohol use seems to shift disease onset earlier rather than hasten progression of disease once clinically evident.

Mechanisms by which smoking and heavy alcohol use may influence age of onset in MSA patients are uncertain. Alcohol is a neurotoxin, especially affecting the cerebellum with oxidative stress, excitotoxicity, and nutrition-related mechanisms potentially contributing to cell loss [10]. In our study, ataxia was more common in heavy alcohol users. Orthostatic intolerance was also common in heavy alcohol users with a smoking history suggesting vasodilatory properties of alcohol may contribute to orthostatic hypotension in MSA. Further questions include whether alcohol's toxic effects on the cerebellum and propensity to worsen orthostatic intolerance causes symptoms of MSA to surface earlier or heavy alcohol use favors the development of MSA-C.

Our findings have relevance for other neurodegenerative diseases: an Enroll-HD study showed that substances of abuse, including smoking and alcohol use, influenced age of motor onset in patients with Huntington's disease [11]. However, smoking is known to be inversely associated with a lower Parkinson's disease (PD) risk [7]. Additionally, smoking has been associated with a later age of onset for both motor and non-motor features in PD [8]. While PD and MSA both represent synucleinopathies, differences in disease pathophysiology and neuropathology may contribute to a differential effect of smoking in MSA.

Strengths of this study include the large MSA cohort and prospective, standardized, and self-reported assessment of smoking and alcohol use which reduces recall bias and provider bias. Limitations include the inability to determine length of alcohol use and cumulative

**Table 1**  
Characteristics of MSA patients with smoking and heavy alcohol use compared to controls.

	MSA Control Group (249)	MSA with Smoking History and no Heavy Alcohol Use (215)	p -value <sup>a</sup>	MSA with Heavy Alcohol Use and no Smoking History (21)	p -value <sup>b</sup>	MSA with both Smoking and Heavy Alcohol Use History (66)	p -value <sup>c</sup>
Sex			0.0116		0.0004		< 0.0001
Male	104 (42%)	115 (53%)		17 (81%)		51 (77%)	
Female	145 (58%)	100 (47%)		4 (19%)		15 (23%)	
MSA Subtype			0.8826		0.0665		0.2744
MSA-P	158 (63%)	135 (63%)		9 (43%)		37 (56%)	
MSA-C	91 (37%)	80 (37%)		12 (57%)		29 (44%)	
Age at onset	62.97 (10.316)	60.76 (9.055)	0.0144	56.87 (10.006)	0.0133	59.36 (8.054)	0.0029
Age at death	70.73 (10.213)	68.43 (8.799)	0.0205	61.98 (8.971)	0.0031	64.55 (8.060)	< 0.0001
Disease duration	7.65 (3.585)	7.26 (3.312)	0.2758	6.88 (3.839)	0.4820	6.80 (2.607)	0.0641
Clinical characteristics							
Orthostatic intolerance	158 (63%)	142 (66%)	0.5600	17 (81%)	0.0913	52 (80%)	0.0091
Bladder symptoms	207 (83%)	180 (84%)	0.8651	15 (71%)	0.2038	55 (85%)	0.7730
Urinary catheter use	33 (13%)	40 (19%)	0.1149	3 (14%)	0.8946	13 (20%)	0.1845
Falls	174 (70%)	138 (64%)	0.1928	15 (71%)	0.8812	47 (72%)	0.7012
Parkinsonism	193 (78%)	165 (77%)	0.8447	16 (76%)	0.8902	40 (62%)	0.0110
Ataxia	112 (45%)	106 (50%)	0.3437	16 (76%)	0.0056	41 (63%)	0.0106
Stridor	55 (22%)	65 (30%)	0.0459	7 (33%)	0.2583	21 (32%)	0.0943
Dream enactment behavior	107 (43%)	95 (44%)	0.7925	12 (57%)	0.2110	32 (49%)	0.3667

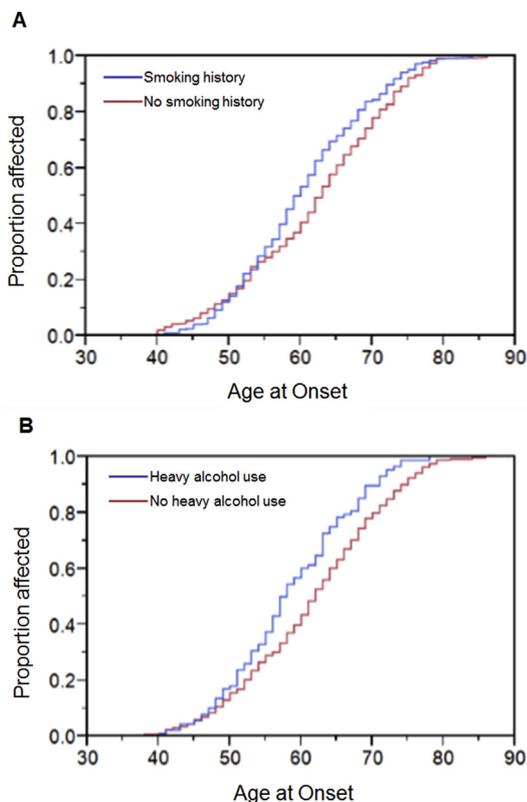
Legend: Continuous variables are represented as mean (standard deviation). Categorical variables are shown as number (percentage).

Abbreviations: C, cerebellar; MSA, multiple system atrophy; P, parkinsonism.

<sup>a</sup> Comparing MSA patients with a smoking history to control MSA patients (no history of alcohol or smoking use).

<sup>b</sup> Comparing MSA patients with heavy alcohol use to control MSA patients.

<sup>c</sup> Comparing MSA patients with both heavy alcohol and smoking use history to MSA control patients.



**Fig. 1.** Influence of smoking and alcohol use on age of onset in multiple system atrophyCensored

Kaplan-Meier survival curves showing the probability of disease onset and age in patients with a history of A) any smoking (blue) compared to no smoking history (red) and B) heavy alcohol use (blue) compared to moderate or no alcohol use (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exposure as cumulative smoking exposure. Data was also not collected on smoking and alcohol use during the course of the disease and whether this may influence survival. Additional possible risk factors such as illicit substance abuse, caffeine use, or comorbid medical conditions were not obtained. In addition, diagnostic accuracy is a possible limitation given that MSA was a clinical diagnosis in a majority of cases.

Further prospective, longitudinal studies may be useful in assessing the effect of different lengths of exposures to smoking and heavy alcohol use on disease onset and progression in MSA.

**Authors’ roles**

Lauren Jackson, M.D.; Study concept and design, acquisition of data, analysis and interpretation, drafting of manuscript.

Elizabeth A. Coon, M.D.; Study concept and design, acquisition of data, analysis and interpretation, drafting of manuscript.

J. Eric Ahlskog, Ph.D., M.D.; Analysis and interpretation, critical revision of manuscript for important intellectual content.

James H. Bower, M.D.; Analysis and interpretation, critical revision of manuscript for important intellectual content.

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**Disclosures**

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