Published in final edited form as:

Mov Disord. 2014 September ; 29(10): 1316–1319. doi:10.1002/mds.25950.

Individual and joint prevalence of three non-motor symptoms in the US general population

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Abstract

Background—Some non-motor symptoms may precede the clinical diagnosis of Parkinson's disease (PD) by years.

Methods—We examined the individual and joint prevalence of depression, daytime sleepiness, and infrequent bowel movement among 10,477 participants of the US National Health and Nutrition Examination Surveys 2005-2008.

Results—For all symptoms, the prevalence was higher in women than in men. Importantly, few participants had two or more symptoms: 1.3% at ages 20-29, 1.0% at 30-39, 1.2% at 40-49, 3.5% at 50-59, 1.7% at 60-69, 1.1% at 70-79, and 1.2% at ages 80 in men; the corresponding prevalence in women was 3.1%, 5.2%, 5.7%, 4.1%, 3.1%, 2.3%, and 1.2% respectively. In both men and women, depression was correlated with infrequent bowel movement and daytime sleepiness, but the latter two were mutually independent.

Conclusion—The presence of multiple nonmotor symptoms was uncommon in the general population and the prevalence was higher in women than in men.

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Author Roles: 1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

Chen: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

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Full Financial Disclosures of all Authors for the Past Year: Drs Chen, Huang, Guo, and Peddada reported no relevant conflict of interest.

Introduction

Accumulating evidence suggests that several non-motor symptoms may precede the clinical diagnosis of Parkinson's disease (PD) by years¹, including hyposmia², constipation³⁻⁵, depression⁶, anxiety^{7, 8}, daytime sleepiness^{9, 10}, and rapid eye movement sleep behavior disorder (RBD)^{11, 12}. Research on these “pre-motor” symptoms may eventually lead to a better understanding of the prodromal stage of PD. While these symptoms are not specific to PD, one may hypothesize that, among future PD cases, multiple pre-motor symptoms may develop over time and become clinically evident several years prior to PD diagnosis. On the other hand, individuals at low risk for PD may also suffer from these symptoms, but their symptoms are more independent of each other and more randomly distributed over the entire life period¹³. This entails research on pre-motor symptoms not only among high-risk populations, but also among the general population who are at low risk for PD. We therefore examined the individual and joint prevalence of selected PD pre-motor symptoms among participants of the U.S. National Health and Nutrition Examination Survey (NHANES) survey.

Methods

Study population

The NHANES survey employs a complex, multistage probability sampling strategy to obtain nationally representative data on health and nutrition. The survey includes an in-home interview on general health, diet, and lifestyle and a health examination at a mobile examination center (MEC). All participants provided written consent and all interviews and examinations were carried out by trained technicians. The current analysis was limited to 10,477 participants, ages 20-85 years, of the NHANES 2005-2008 MEC survey with non-missing data on at least one of the three pre-motor symptoms described below.

Symptoms assessments

Depression

NHANES used the well-validated 9-item Patient Health Questionnaire (PHQ-9) to screen for depression among participants 12 years or older^{14,15}. The PHQ-9 score ranges from 0 to 27, and a score of 10 indicates “moderate to severe depression”¹⁴.

Infrequent bowel movement

NHANES participants age 20 years and older were asked to report the number of bowel movements per week. Answers ranged from 1 to 70 and we considered 3 per week as infrequent.

Daytime sleepiness

A question on daytime sleepiness was asked for participants 16 years or older: “In the past month, how often did you feel excessively or overly sleepy during the day?” Possible answers were never, rarely (1 time), sometimes (2-4 times), often (5-15 times), and almost

always (16-30 times). We defined daytime sleepiness as almost always sleepy during the day.

Statistical analysis

Analyses were conducted among 5,080 men and 5,397 women ages 20 years or older. We calculated the age- and gender-specific prevalence and 95% confidence intervals (CI) of each pre-motor symptom as defined above. This analysis was carried out using the Survey procedure in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina) after accounting for MEC sampling weights. We then calculated the prevalence of 2 symptoms for each age group. Assuming Poisson distribution, we use loglinear models to test the null hypothesis of pair-wise independence of these symptoms. Since few participants (3 men and 25 women) had all three symptoms, we only examined pairwise dependence between two symptoms modeled as the interaction term in loglinear models and a P for interaction <0.05 indicates a lack of independence.

It is possible that these symptoms in prodromal PD are relatively mild, we therefore conducted a secondary analysis using “milder” cutoffs: PHQ-9 ≤ 5 for any depression, <1 /day for infrequent bowel movement, and >5 times/month for daytime sleepiness. All statistical tests were based on two-sided α of 0.05.

Results

The overall prevalence in men was 5.0% (95% CI: 4.0-6.0%) for depression, 5.1% (4.2-6.0%) for daytime sleepiness, and 3.7% (2.9-4.5%) for infrequent bowel movement; higher prevalence was found in women: 8.5% (7.3-9.7%), 6.9% (6.0-7.8%), and 11.3% (10-12.6%) respectively. In both men (Figure 1) and women (Figure 2), the prevalence of depression peaks in mid-adulthood and then decreases over age. In men, the prevalence of infrequent bowel movement is lower in middle age than in other age groups; in contrast a clear trend of decreasing prevalence with age is observed among women until 80 years or older. The prevalence of daytime sleepiness is relatively stable over age in men; in women, the prevalence peaks in ages 30-39 and then decreases gradually with age until 80 years or older.

The joint prevalence of 2 symptoms remains low ($<2.0\%$) in men throughout lifetime with the exception of ages 50-59 (3.5%). In women, the joint prevalence gradually goes up until ages 40-49 and then decreases persistently into older age groups. The joint prevalence was higher in women than in men across all age groups until ages 80-85.

In both men and women, depression was related to infrequent bowel movement (P for interaction <0.0001) and daytime sleepiness (P for interaction = 0.01 for men and <0.0001 for women). Infrequent bowel movement and daytime sleepiness on the other hand were not related (P for interaction = 0.83 for men and 0.51 for women).

As expected, the secondary analyses with “milder” cutoffs showed higher prevalence: 17.4% (16.0-18.9%) in men and 25.5% (23.5-27.5%) in women for any depression, 15.4% (14.0-16.7%) and 21.4% (19.5-23.2%) for >5 times/month of being sleepy during the day,

and 8.8% (7.6-10.0%) and 21.6% (20.0-23.3%) for <1 bowel movement per day. The joint prevalence was 7.5% (6.4-8.5%) in men and 13.2% (11.7-14.7%) in women for two symptoms, and 0.8% (0.5-1.1%) in men and 2.7% in women (2.0-3.3%) for three symptoms. The joint prevalence for 2 symptoms was relatively stable (<10%) in men throughout adulthood, and decreases consistently over age in women from 19.3% for ages 20-29 to 9.2% for ages 80 or over. Correlation analysis again showed significant relationships only between depression and the other two symptoms (P for interaction 0.001 for both men and women).

Discussion

Research on “pre-motor” symptoms of PD may hold the potential for early disease identification and a better understanding of disease etiology. However, such effort has been impeded by the fact that none of these symptoms, with the possible exception of RBD¹⁶, are specific to PD^{17, 18}. On the other hand, the development of multiple symptoms in the same individual may reflect a common disease process, for example, synucleinopathies at various parts of the nervous system that may eventually progress to PD¹⁹. In the absence of common pathogenesis, these symptoms also occur, but they are unlikely to cluster in the same individual¹³. Therefore the presence of multiple premotor symptoms may be much more specific in predicting PD than individual symptoms. As a proof of concept, the Honolulu Asia Aging Study reported that 2 of the 24 individuals with three prodromal symptoms developed PD a few years later, as compared with 8 out of 852 for those with only one symptom¹⁷.

Our data provide background information that may facilitate future research on PD pre-motor symptoms. First, in the US general population, the joint prevalence of 2 of these pre-motor symptoms was relatively low in later adulthood, particularly in men. Further, we found potential gender differences in symptom prevalence. For both individual and multiple symptoms, the prevalence was much higher in women than in men, particularly in younger age groups. These differences may reflect the heterogeneous natures of these symptoms and/or differential risk profiles by gender. Further, the prevalence of multiple pre-motor symptoms was relatively stable in men over age, but decreases over age in women.

Our analyses showed that depression was correlated with infrequent bowel movement and daytime sleepiness in both men and women, whereas the other two were mutually independent. Correlations of depression with the other two symptoms are expected as it is known that sleep disorders and functional bowel diseases are associated with neuropsychological symptoms such as depression and anxiety^{20, 21}. Future studies should include other important pre-motor symptoms such as hyposmia and RBD, and examine whether the correlations among these symptoms show different patterns between PD patients and controls.

Other limitations of the study include the cross-sectional nature of this analysis and the small number of participants with multiple symptoms for certain age and gender groups. Further, the NHANES has only screening questions for daytime sleepiness and constipation,

and thus may not accurately reflect their prevalence. Ideally these symptoms should be evaluated via structured questionnaires or clinical examination.

Nevertheless this study provides background data on three pre-motor symptoms in the general population. A careful evaluation of multiple pre-motor symptoms in populations at various risks for PD may eventually lead to a better understanding of early development of the disease.

Acknowledgments

We thank Dr. Barry Graubard at the National Cancer Institute for his comments on statistical analyses.

Funding: This research was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences.

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Figure 1. Age-specific prevalence of non-motor symptoms in men, NHANES 2005-2008

Figure 2. Age-specific prevalence of non-motor symptoms in women, NHANES 2005-2008